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EXPERIENCES WITH ANGIOGRAPHY AS A GUIDE TO MEDIASTINAL EXPLORATION

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and
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The question whether a given mediastinal lesion is amenable to surgery is not always answerable by roentgenograms or by fluoroscopy. Often the only accurate means of distinguishing vascular from nonvascular lesions is provided by angiocardiography and thoracic aortography. The techniques here described were used in obtaining 188 angiocardiograms and 17 thoracic aortograms in 200 patients. The value of the information so obtained in planning surgical procedures, if any, is illustrated by 12 case histories.

THE diagnosis and treatment of lesions of the mediastinum have long been challenging problems to the physician. Although surgical exploration of the mediastinum can now be accomplished with minimal risk to the patient, it is still attended by a rather high morbidity and a significant, albeit small, mortality. Therefore, it is obviously desirable to be able to determine, without exploration, the nature and extent of any existing mediastinal lesion. Unnecessary surgical procedures thus can be avoided and intelligent surgical planning and reduction of mortality, accomplished. This consideration is of increasing importance today, in view of the fact that many vascular lesions of the mediastinum which formerly were inoperable are now amenable to surgical treatment.

While roentgenographic examination of the thorax is highly accurate in detecting the presence of mediastinal lesions, the roentgenographic findings frequently are not specific enough to permit determination of the exact nature and extent of lesions [illegible] revealed. It is particularly difficult to distinguish between vascular lesions and mediastinal tumors, cysts, or granulomas when these lesions are located in close proximity to the great vessels. In the past fluoroscopy was thought to be an accurate means of differentiating vascular from nonvascular lesions. When observed fluoroscopically, vascular lesions are supposed to show expansile pulsation and nonvascular lesions either no pulsation at all or a transmitted (nonexpansile) type of pulsation. In our experience, however, fluoroscopy has proved inaccurate in making this differentiation. It is a well-known fact that aneurysms may not show any pulsation whatsoever at fluoroscopy, and that cysts.

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Angiocardiography and thoracic aortography often provide the only accurate means, short of thoracotomy, of differentiating vascular from nonvascular lesions of the mediastinum. Furthermore, the exact nature and extent of all vascular lesions may be easily determined by these angiographic methods and their operability or inoperability may be more clearly defined. If a mediastinal mass is shown by angiography to be separate from the vascular system, then surgical exploration and histological examination of removed tissue are the only means of differentiating between granulomatous, cystic, and neoplastic lesions.

While the use of angiocardiography and thoracic aortography in the diagnosis of congenital heart disease has in recent years captured the interest of the physician, much less attention has been given to the use of these techniques, particularly aortography, in the study of lesions of the mediastinum.[1] The material for this report is drawn from experiences with angiocardiography and thoracic aortography in the study of 200 patients seen at the Mayo Clinic with a variety of mediastinal problems. Our experience would support that of others who have found these methods to be safe and rewarding when used to investigate this type of problem.

Methods

Angiocardiography.—In the study of this group of patients, angiocardiography has been performed with few exceptions by the intravenous method, with injection through a needle inserted percutaneously into an antecubital vein. In a few instances the examination has been carried out by passing a cardiac catheter into an antecubital vein and thence into the superior vena cava or right ventricle, the injection being made into one of these chambers. In the study of most mediastinal problems, selective technique has no advantages over intravenous method. The intravenous method simpler and is, of course, preferable in those cas in which there is suspected involvement of th superior vena cava.

Patients are prepared by withholding food and fluids for at least six hours before the examination. Premedication is not always necessary, but apprehensive patients are given meperidine (Demerol) hydrochloride one-half to one hour beforehand. No anesthesia is required except for a local anesthetic at the site of puncture or cut-down on the antecubital vein.

If a single-plane examination is made, the choice of projection is important. From a study of the posteroanterior and lateral views of the thorax, a projection is selected which would seem to show the mass in question and the great vessels to the best advantage. In general, the aorta and lesions to be differentiated from the aorta are best studied in the lateral or left anterior oblique projection, while the pulmonary arteries and lesions in proximity to them are best studied in the anteroposterior projection. In some instances it will be necessary to make two injections and to make films in more than one projection. When biplane equipment is used, the examination is usually carried out in the anteroposterior and lateral projections. In every case a preliminary film is made to check positioning and technique before the examination is begun.

A 70% solution of sodium acetrizoate (Urokon Sodium) has been the contrast material used oftenest in our work. Recently, we have tried 75% diatrizoate (Hypaque) sodium and 85% methylglucamine diatrizoate (Cardiografin) with success. We have noted that, while contrast is possibly a little better with use of sodium acetrizoate, the unpleasant side-reactions are less pronounced with diatrizoate sodium and methylglucamine. The use of 1 cc. of medium per kilogram of body weight is us-

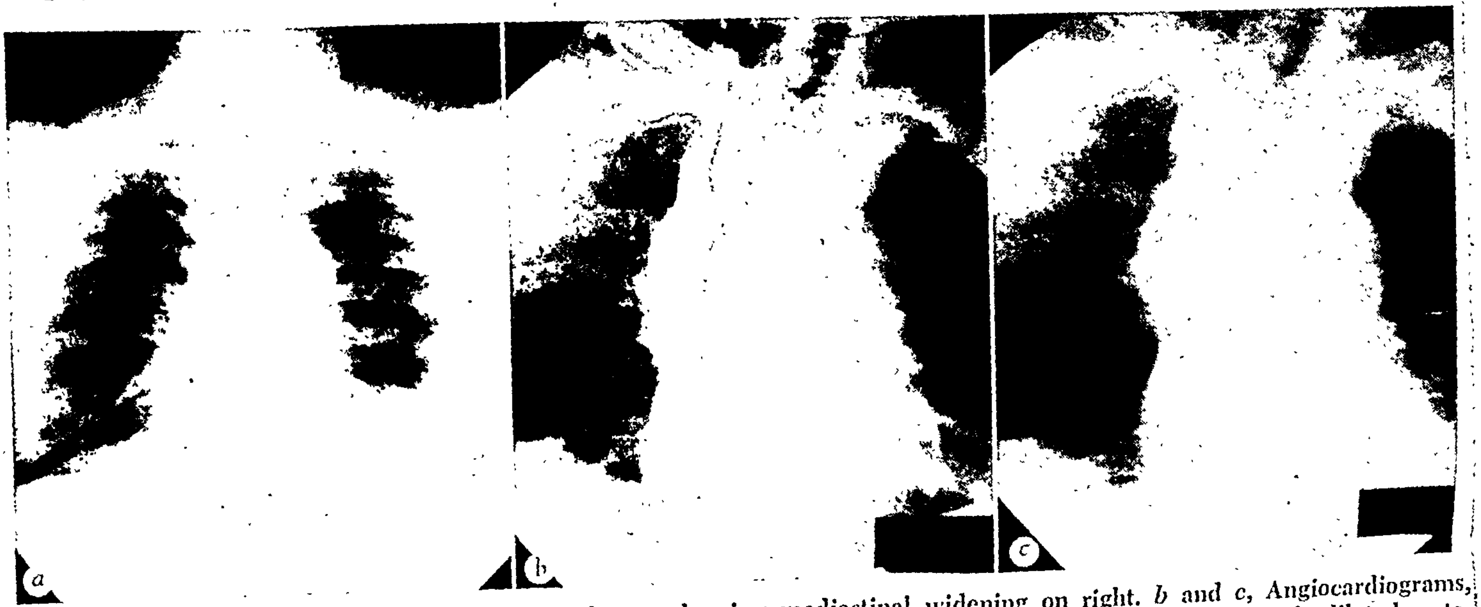

Fig. 1 (case 1).—*a*, Posteroanterior view of thorax, showing mediastinal widening on right. *b* and *c*, Angiocardiograms, revealing widening to be due to superior vena cava which is displaced to right by tortuous and somewhat diffusely dilated aorta.

ually accepted as standard, but we have never found it necessary to use more than 70 cc. per injection, even in large adults. In the study of patients with suspected obstruction of the superior vena cava, 20 to 25 cc. of contrast material usually will suffice to demonstrate the superior vena cava and right side of the heart.

The injection of medium should be made as rapidly as possible and can usually be accomplished within three seconds. With the intravenous method the injection is made by hand, but when the injection is made selectively through a catheter, some type of automatic injector is necessary.

In the evaluation of mediastinal problems high-speed serial filming, such as that which is necessary in the study of congenital heart disease, is not required. Serial filming at rates of more than two films per second is never needed, and the examination may be carried out satisfactorily with use of a relatively inexpensive single-plane cassette changer.

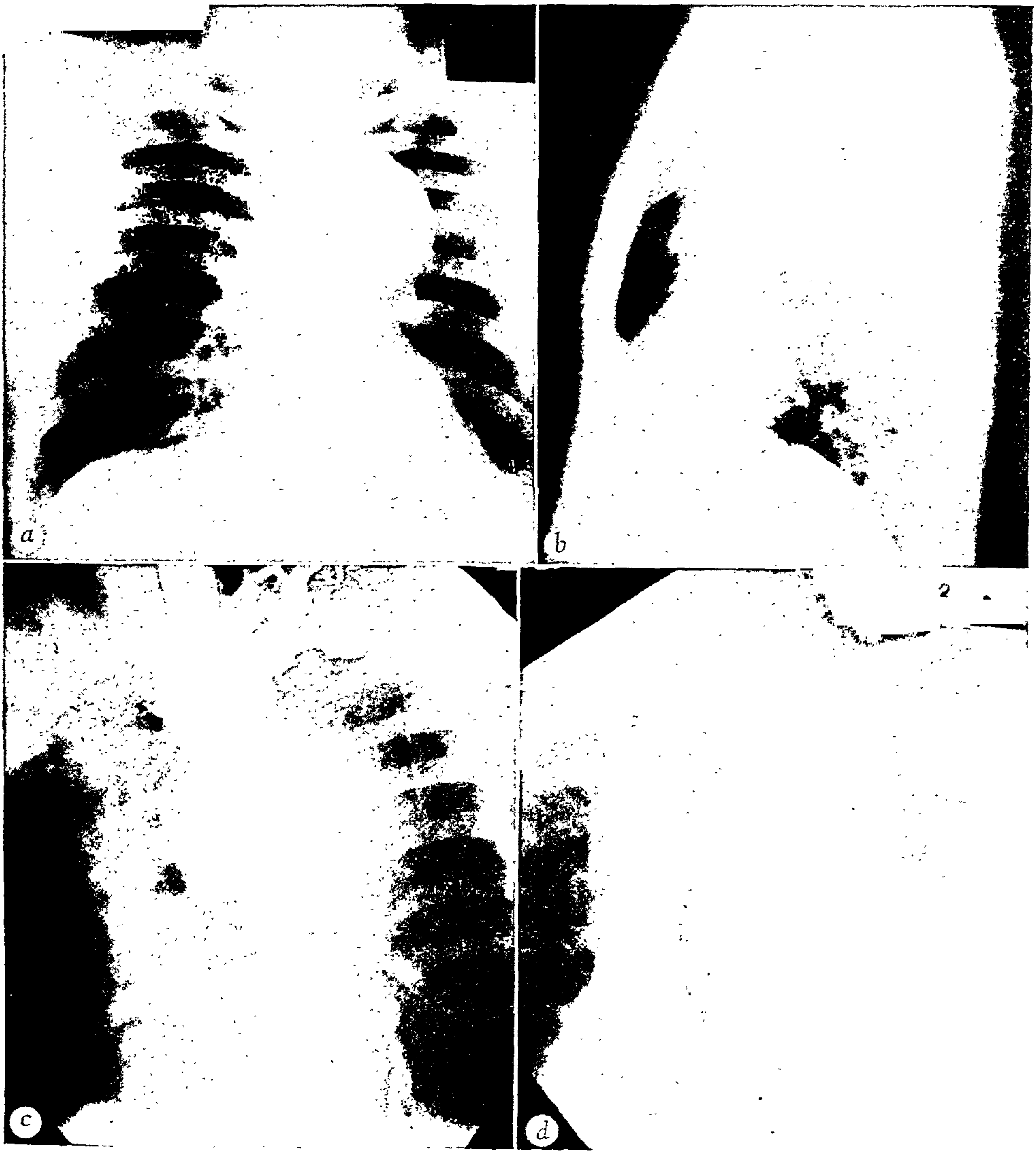

Fig. 2 (case 2).—*a* and *b*, Posteroanterior and lateral views of thorax, showing rounded mediastinal mass
aortic arch. *c*, Angiocardiogram, showing compression of superior vena cava by the mass. *d*, Thoracic
to be an aneurysm arising distal to origin of left subclavian artery; brachiocephalic vessels are not invol

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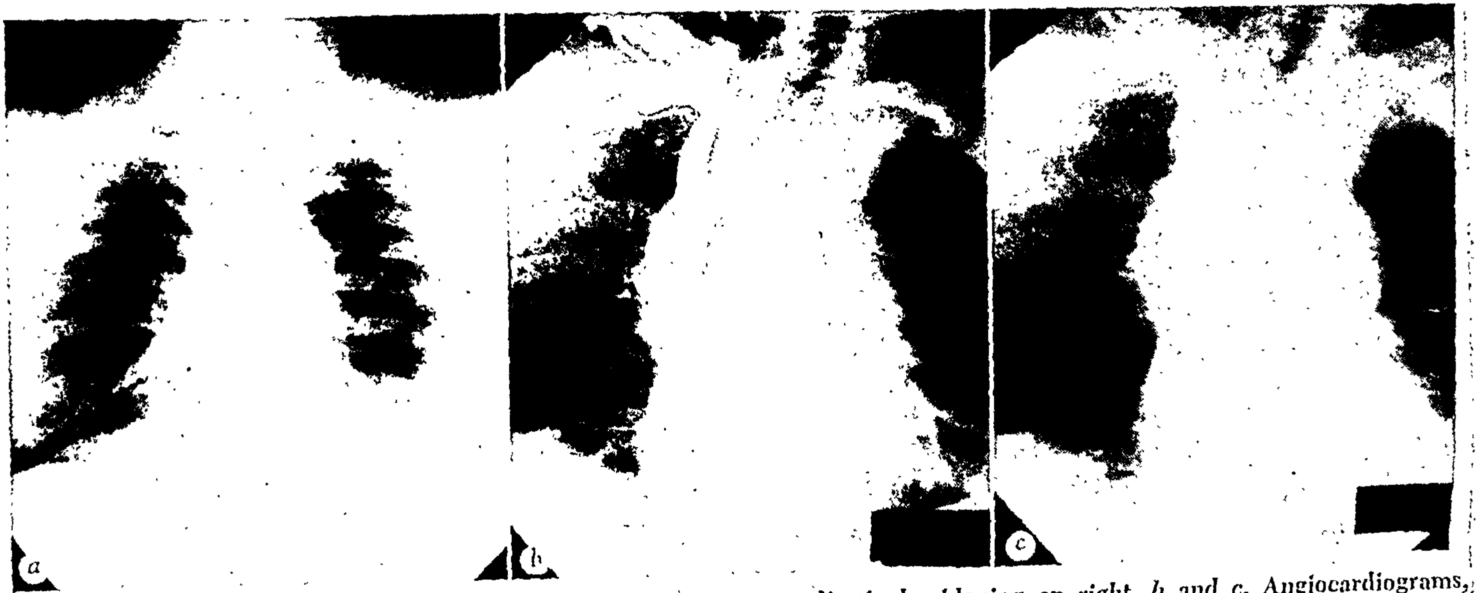

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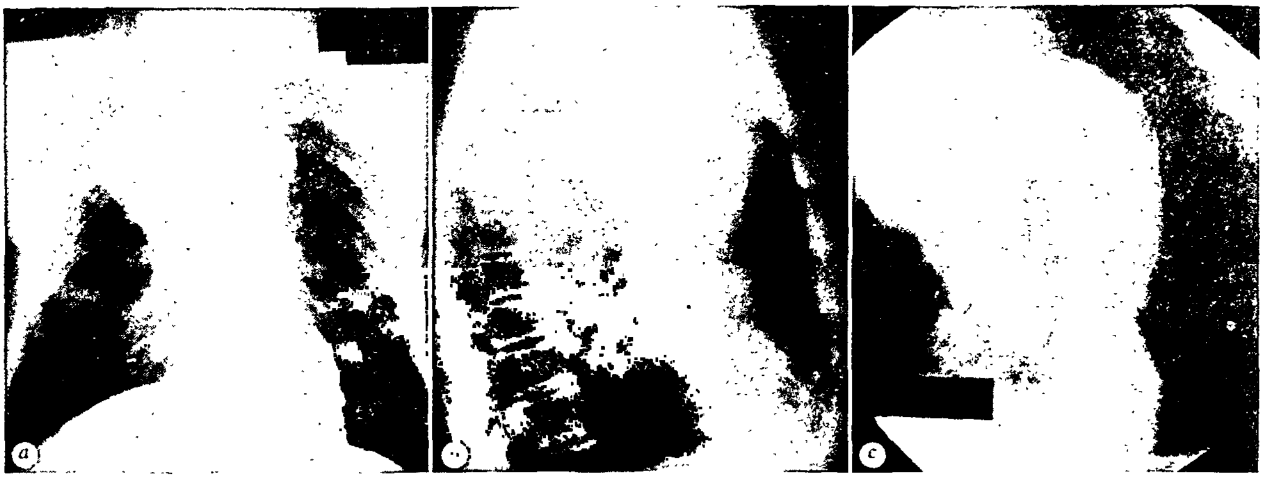

Fig. 4 (case 4).—*a* and *b*, Posteroanterior and lateral views, showing mediastinal mass somewhat similar to that seen in case 3. *c*, Thoracic aortogram, showing mass to be separate from aorta; extensive atheromatous changes involve aorta.

Thoracic aortography may be carried out by several different methods. The technique of retrograde aortic catheterization is less hazardous and less difficult than either direct needle puncture of the aorta or of the left ventricle and, in our opinion, is the technique of choice.[2] In this method cut-down is performed on either the femoral or radial artery and a cardiac catheter is passed into the aorta so that its tip lies in the midascending aorta or at whatever point seems most desirable. The patient is then positioned over the film changer and a preliminary film is made. Thoracic aortography is best carried out with the patient in the left anterior oblique or lateral position when single-plane examination is performed. Although 1.0 to 1.2 cc. of contrast medium per kilogram of body weight has been suggested by some workers, we have not found it necessary to use more than 50 cc. per injection for thoracic aortography, even in large adults. This is injected through the catheter in two to three seconds by means of a pressure injector, and serial filming is carried out as with angiocardiography. The examination may be carried out with the patient under general anesthesia or with the use of local anesthesia only at the site of the arterial cut-down.

Results

In 200 patients having a variety of mediastinal problems, 188 angiocardiograms and 17 thoracic aortograms had been carried out. Five patients on whom thoracic aortograms were performed had previously had angiocardiograms which were unsuccessful.

Angiocardiography was considered technically successful in 173 (92%) of the patients examined by this method. In six patients the examination was unsuccessful because of compression and partial obstruction of the superior vena cava or innominate vein by the mass under study. In eight other patients the examination was unsuccessful due to lack of adequate aortic opacification. Adequate opacification of the thoracic aorta by intravenous angiocardiography was more difficult to obtain in large patients. One examination was unsuccessful because of the inadvertent injection of a portion of the opaque medium into the antecubital perivascular soft tissues. Thoracic aortography was successful in all 17 (100%) cases in which it was performed.

The accuracy of the various diagnostic techniques used in the study of this series of patients is summarized in the accompanying table. It is obvious from the figures shown that fluoroscopy is often inaccurate in the differentiation of vascular from nonvascular mediastinal lesions. In a number of patients a mediastinal mass was described at fluoroscopy as showing expansile pulsation only to prove to be a nonvascular lesion. Conversely, in several patients a mass which proved to be vascular was described as showing only transmitted pulsation or, in a few instances, no pulsation at all. The diagnostic accuracy of angiocardiography in differ-

Differentiation of Vascular and Noncascular Lesions of Mediastinum: Accuracy of Techniques

Techniques*	Satisfactory Examinations, No.	Result: Correct	Result: Indeterminate	Result: Wrong	Accuracy, %
Fluoroscopy	102	28	48	26	28
Angiocardiography	173	173	0	0	100
Thoracic aortography	17	17	0	0	100
Tomography	10	0	10	0	0
Bronchoscopy	17	1†	16	0	6

* Cytological investigation was carried out in five cases of malignant tumor; one specimen showed positive results.
† Biopsy showed carcinoma in one case.

Thoracic Aortography.—In our opinion, angiocardiography is potentially a safer procedure than thoracic aortography. Certainly, angiocardiography is a less time-consuming procedure and technically much easier to perform. It has been our practice to perform angiocardiography in almost all mediastinal problems and to reserve thoracic aortography for those few cases in which visualization of the thoracic aorta is necessary but not satisfactory by means of angiocardiography. In those cases, however, in which the diagnosis of aneurysm of the thoracic aorta or innominate artery seems well substantiated beforehand and in which angiography is performed primarily for surgical evaluation, it is probably best to perform thoracic aortography initially. By aortography the extent of such aneu-

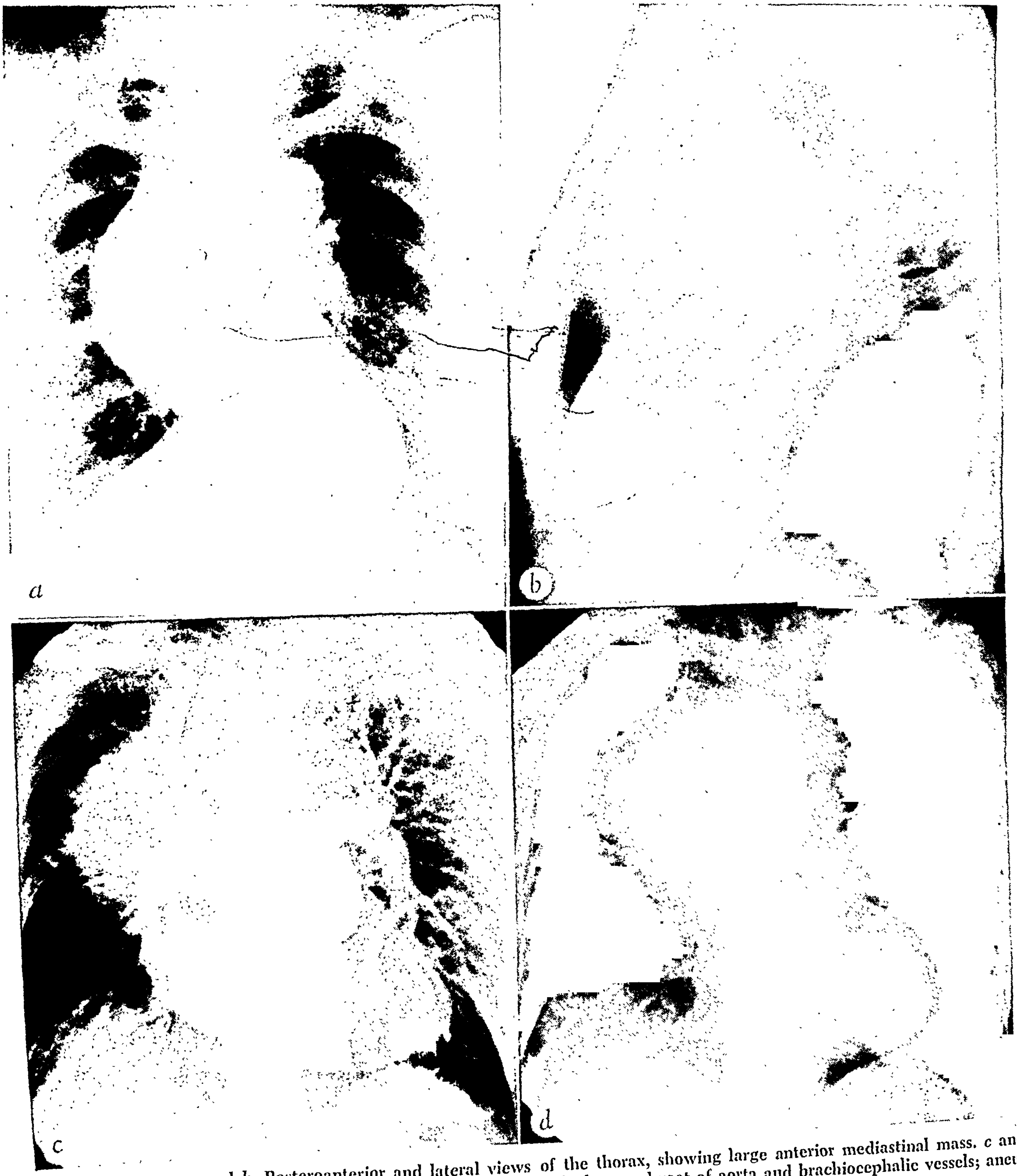

Fig. 3 (case 3).—*a* and *b*, Posteroanterior and lateral views of the thorax, showing large anterior mediastinal mass. *c* and *d*, Angiocardiograms showing huge aneurysm of ascending aorta which spared root of aorta and brachiocephalic vessels; aneurysm was felt to be operable.

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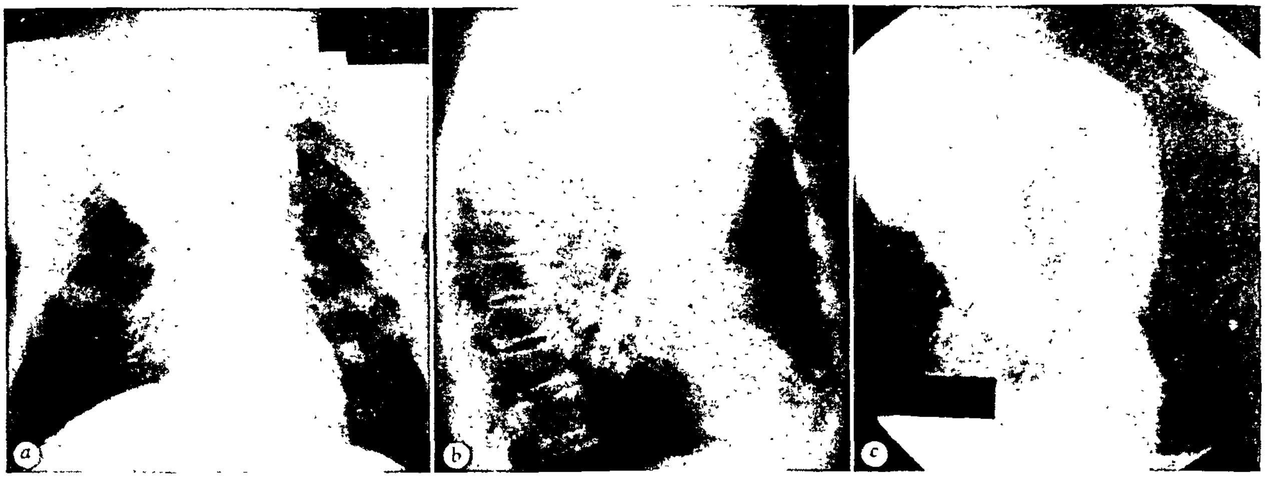

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entiating vascular from nonvascular lesions of the mediastinum, in those cases in which the examination was technically successful, was 100%. Thoracic aortography was also 100% accurate in making this differentiation.

Tomography was used too infrequently for critical evaluation but was not helpful in the few instances in which it was used. Bronchoscopy was performed infrequently and was of little help, as might be expected in a series of patients who had largely vascular lesions and benign tumors or cysts. Cytologic examination of bronchial washings was also carried out infrequently in this series of patients and showed positive results in only one of five cases of malignant tumor, four of which were bronchogenic carcinomas.

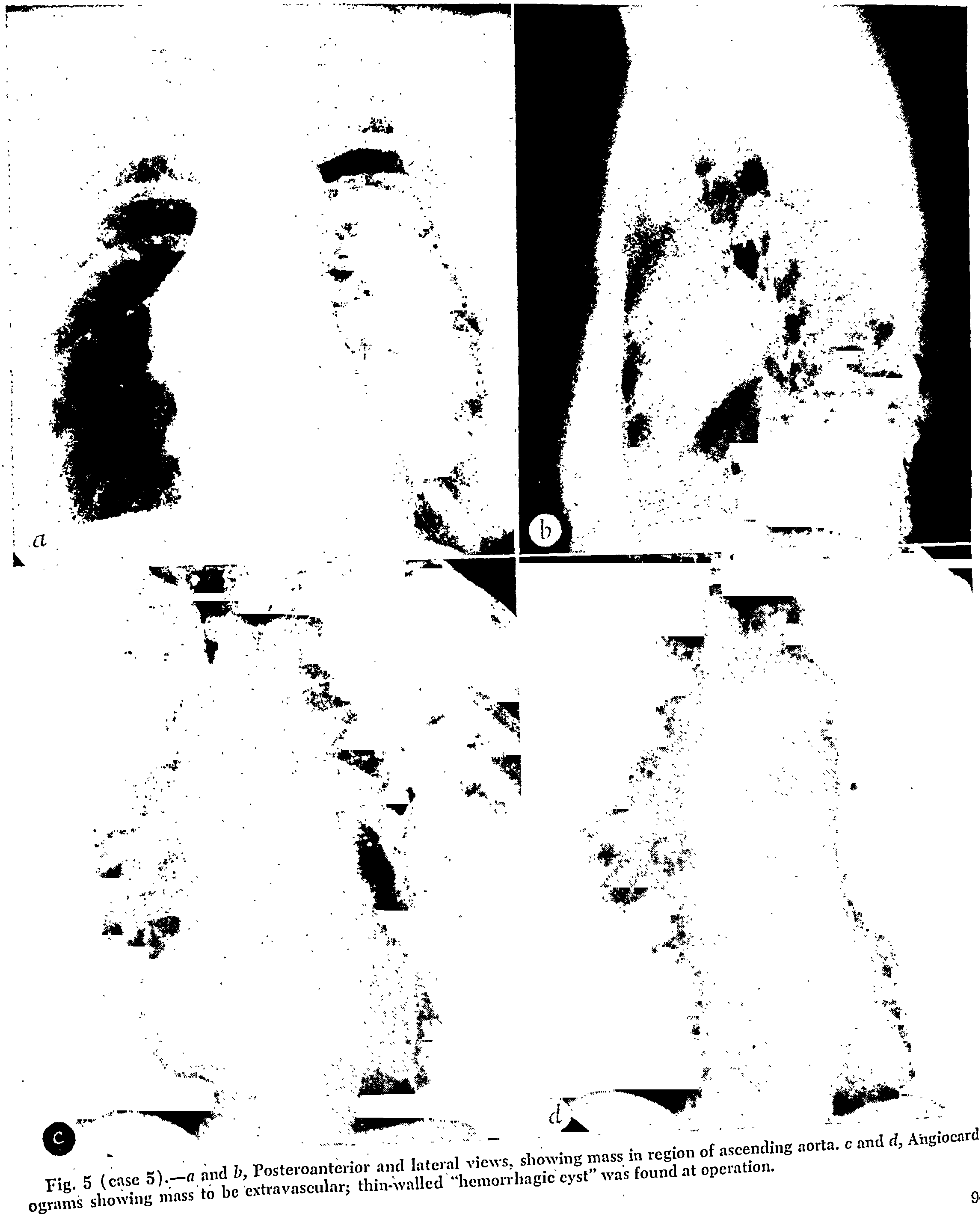

Fig. 5 (case 5).—*a* and *b*, Posteroanterior and lateral views, showing mass in region of ascending aorta. *c* and *d*, Angiocardiograms showing mass to be extravascular; thin-walled "hemorrhagic cyst" was found at operation.

No fatalities have occurred and no serious reactions have been encountered in this series of patients when either angiocardiography or thoracic aortography was used. Mild, transitory flushing and a sensation of heat commonly occur at the time of injection, and these reactions are usually more pronounced with aortography than with angiocardiography. Other minor reactions which have been encountered rarely are nausea, mild headache, and hives. Transient edema of the face and hands occurred in one patient after an angiocardiogram. In one instance venospasm occurred, involving the injected antecubital vein, with engorgement of the veins in the forearm and hand distal to the site of injection. This reaction persisted for only a few minutes. Localized phlebitis developed in one other patient after an intravenous angiocardiogram. The one patient in whom the contrast material was injected into the soft tissues of the antecubital space experienced severe pain at the time of injection and for several hours thereafter. The patient's arm remained sore and painful for about 48 hours but tissue necrosis did not occur.

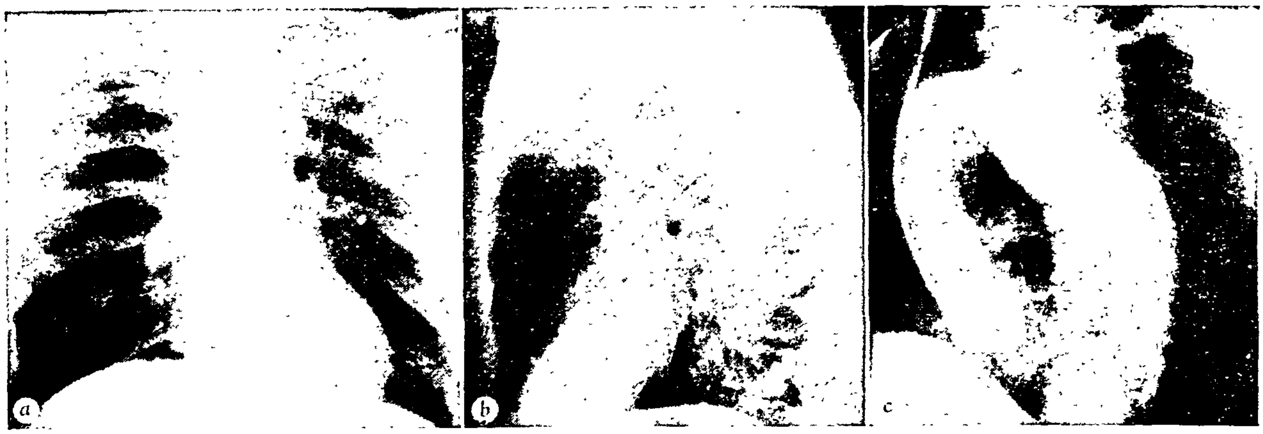

Fig. 6 (case 6).—*a,* Posteroanterior view, showing mediastinal mass on left in region of aortic arch. *b,* Lateral view. *c,* Thoracic aortogram, showing kinking of aortic arch.

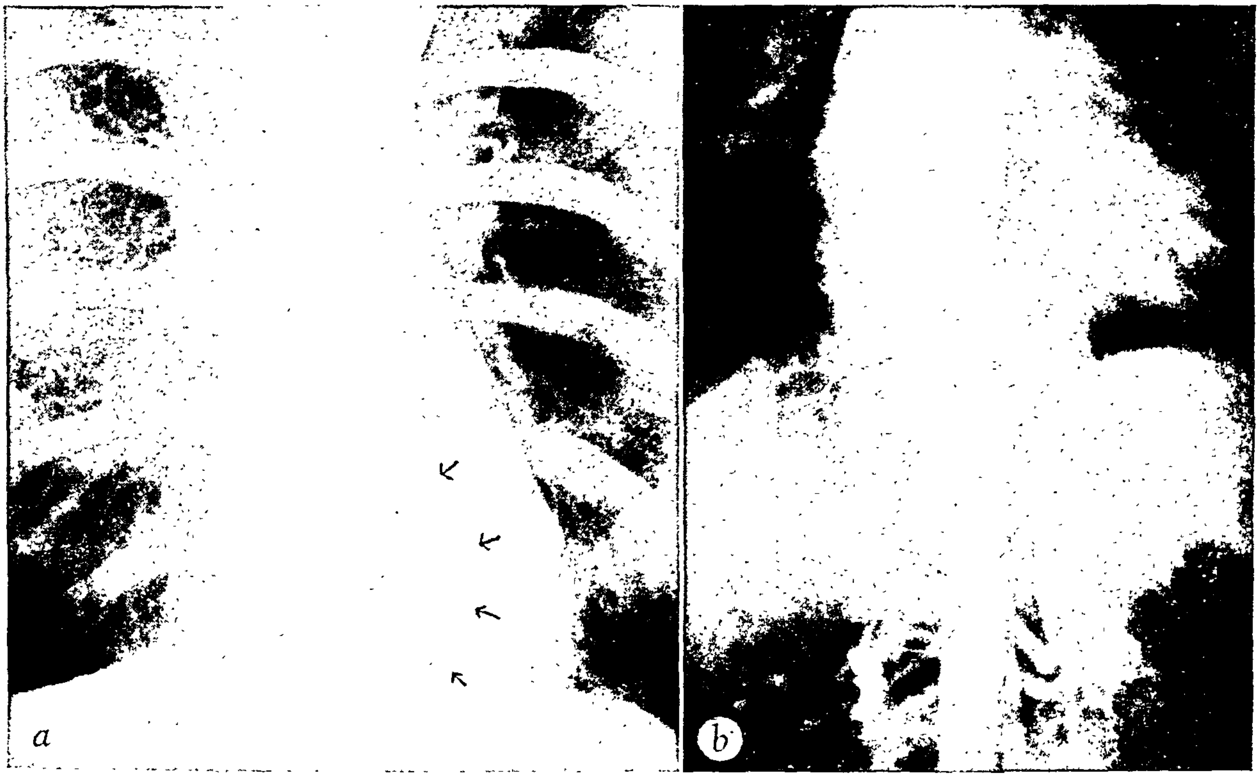

Fig. 7 (case 7).—*a,* Posteroanterior view of thorax, showing rounded mediastinal mass behind heart (*arrows*). *b,* Aortogram with injection through catheter passed from radial artery; lower thoracic aorta is normal and mass is seen to be nonvascular.

Because it is believed that the injection of a second dose of contrast material within a short time after the first injection may increase the hazard of angiography, we avoid such reinjection whenever possible. In only 18 patients comprising the present series was a second injection necessary to demonstrate better the lesion in question. More than two injections were not made in any instance. When relatively smaller doses of contrast material are used, as in the study of patients with suspected obstruction of the superior vena cava, a second or even a third injection probably does not increase the hazard of the procedure significantly.

Report of Cases

Angiocardiography and thoracic aortography have been found of great value in the diagnosis and surgical assessment of a variety of mediastinal problems at the Mayo Clinic. The following cases are representative of the type of abnormalities in which these techniques have been of special usefulness.

Case 1.—A 54-year-old man was referred to the clinic because of vertigo. A thoracic roentgenogram was interpreted as showing mediastinal widening on the right at the level of the hilus (fig. 1*a*). The lesion in question was thought to show transmitted pulsation and suggested the possibility of tumor or enlarged lymph nodes.

Exploration was planned, but an angiocardiogram was performed first because of the remote possibility that this widening might represent an aneurysm of the ascending aorta. Angiocardiography revealed that the mediastinal widening was due to the superior vena cava which was displaced and bowed outward by a tortuous and somewhat diffusely dilated aorta (fig. 1*b* and *c*). Because of the angiocardiographic findings in this patient, unnecessary surgical exploration was avoided.

Case 2.—A 37-year-old man complained of intermittent precordial pain of four days' duration. A roentgenogram of the thorax revealed a mediastinal mass on the left at the level of the aortic arch (fig. 2*a* and *b*). The mass was seen to pulsate, but it could not be determined whether this pulsation was transmitted or expansile. Aortic aneurysm, in spite of the patient's age of 37 years, was thought to be the most likely diagnosis.

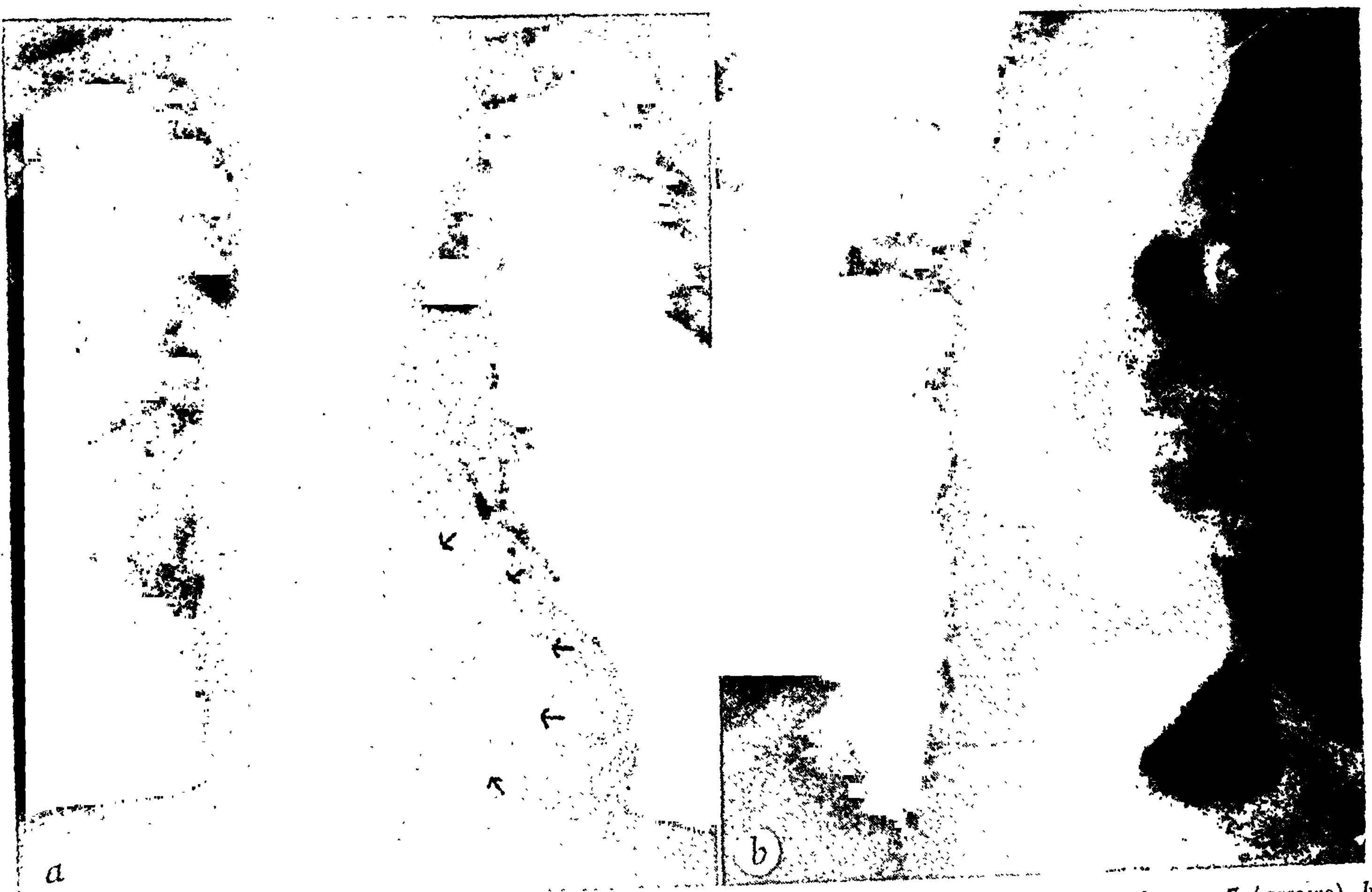

Fig. 8 (case 8).—*a*, Posteroanterior roentgenogram, showing retrocardiac mass similar to that seen in case 7 (*arrows*). *b*, Transthoracic aortogram with injection through needle placed in thoracic aorta. (This method of thoracic aortography is no longer used at the Mayo Clinic, since retrograde aortography by means of a catheter passed into aorta is believed to be easier and safer.) Mass behind heart is seen to be due to extremely tortuous but otherwise normal aorta.

Angiocardiography was unsuccessful because of compression of the superior vena cava by the mass under study (fig. 2*c*). Thoracic aortography was then carried out via the right radial artery and revealed the presence of an aortic aneurysm located just distal to the origin of the left subclavian artery and not involving the brachiocephalic vessels (fig. 2*d*). This is the typical location of aneurysms of congenital and traumatic origin.

On further questioning it was learned that the patient had been a member of the crew of a B-17 bomber which crashed in the sea during World War

II, and it was felt that the aneurysm was probably of traumatic origin.[3] The aneurysm was successfully resected and histologically was found to be of the traumatic type.

In this case, angiography not only established the diagnosis of aneurysm but also, by demonstrating the lack of involvement of the brachiocephalic vessels, provided information which aided the surgeon in planning his operative approach (in this instance, posterolateral) and indicated that bypass shunts would not be necessary.

Case 3.—On routine roentgenographic examination of the thorax, a 47-year-old woman was found to have a large anterior mediastinal mass (fig. 3*a* and *b*). A similar roentgenogram made five years earlier had not shown evidence of any abnormality. At fluoroscopy the mass showed only faint pulsation which did not appear expansile, and the presence of an anterior mediastinal tumor seemed more likely than an aneurysm. A serologic test for syphilis gave positive results. An angiocardiogram revealed the mass to be a huge aneurysm of the ascending aorta. The root of the aorta, the sinuses of Valsalva, and the brachiocephalic vessels were not involved and, therefore, the aneurysm was operable (fig. 3*c* and *d*).

This case demonstrates, as does case 2, the value of angiography not only in the diagnosis of aortic aneurysms but also in the evaluation of operability and as a guide to surgical planning.

Case 4.—A 73-year-old man complained of cough of three months' duration. It was learned that he had had an enlarging intrathoracic mass for at least two years which had been presumed to be an aortic aneurysm.

Roentgenographic examination of the thorax on his admission to the clinic showed the presence of a large anterior mediastinal mass extending to the right (fig. 4*a* and *b*). This mass could not be separated from the aorta but did not show pulsation fluoroscopically.

A retrograde aortogram showed the mass to be a nonvascular lesion (fig. 4*c*). In view of its rapid growth, it was believed to be a malignant neoplasm. Surgical measures were not considered advisable, however, because of the patient's age and general condition, and, therefore, a definite diagnosis was not possible.

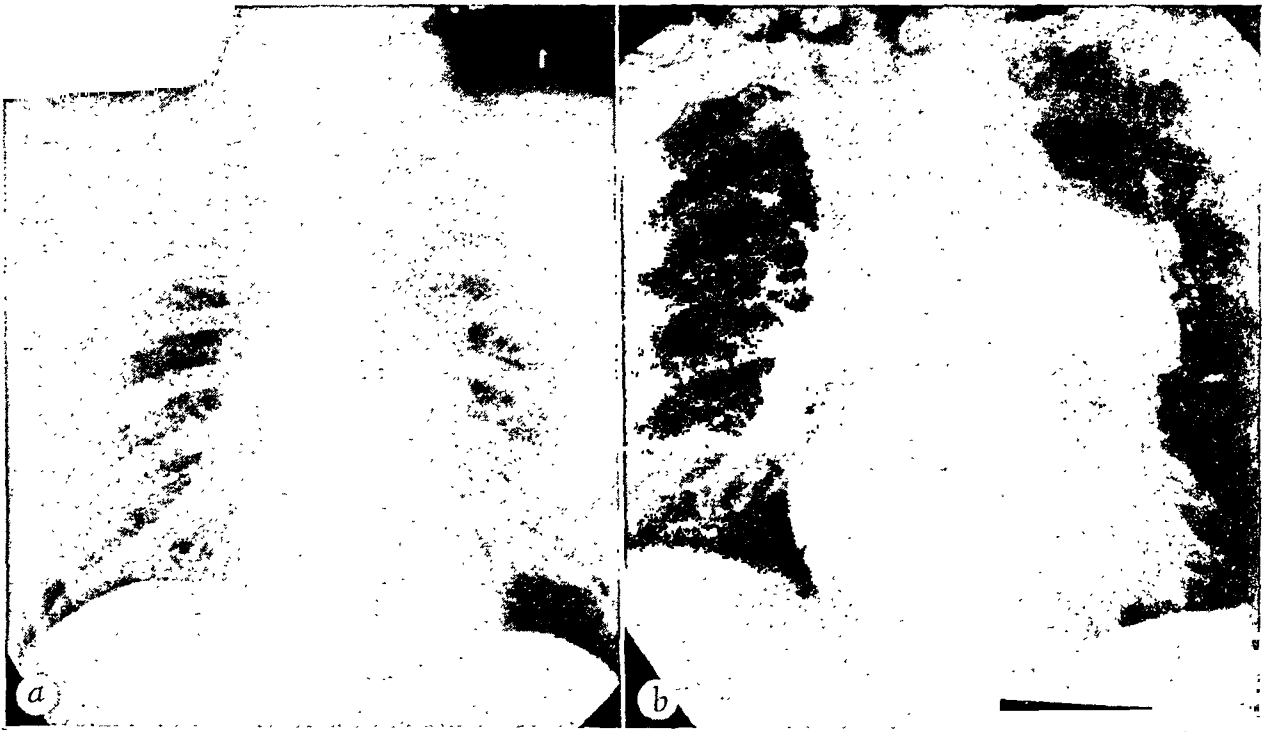

Fig. 9 (case 9).—*a*, Posteroanterior view, showing large left hilar mass. *b*, Angiocardiogram, showing mass to be due to extreme dilatation of pulmonary artery.

Case 5.—A 46-year-old woman complained of pain of three weeks' duration in the right anterior part of the thorax. Hypertension had been present for one year. The results of physical examination were normal. Roentgenographic examination of the thorax revealed the presence of a mediastinal mass on the right in the region of the ascending aorta (fig. 5*a* and *b*).

To distinguish an aneurysm from a mediastinal tumor, an angiocardiogram was performed. It revealed the mass to be a nonvascular lesion (fig. 5*c* and *d*) and surgical exploration was carried out. The lesion proved to be a thin-walled cyst containing blood. It was completely resected. On histological examination no specialized lining could be identified, but a few foci of thymic glandular tissue were present. The exact nature of the cyst, however, could not be determined.

Case 6.—On routine roentgenographic examination of the thorax, a 57-year-old man was found to have a mediastinal mass on the left in the region of the aortic knob (fig. 6*a* and *b*). Fluoroscopy was indeterminate. It seemed likely, however, that the abnormal shadow represented either an aortic aneurysm or a mediastinal tumor.

Angiocardiography did not opacify the aorta satisfactorily and, therefore, a retrograde thoracic aortogram was performed. This showed the abnormal shadow to be due to kinking of the aorta or so-called pseudocoarctation (fig. 6*c*). No treatment was necessary, of course.

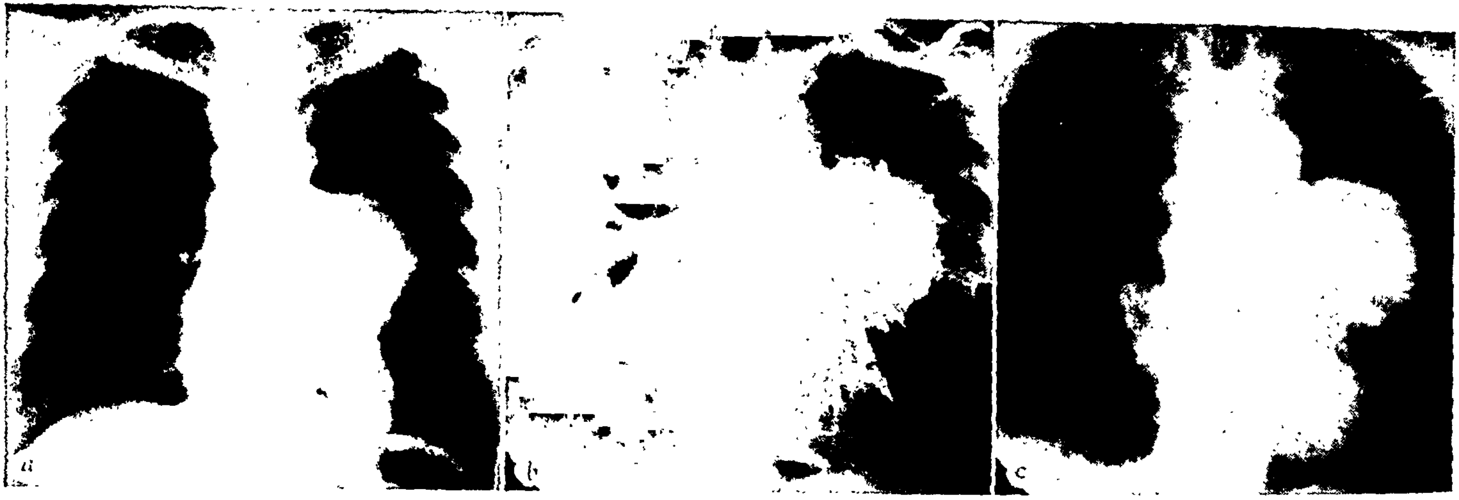

Fig. 10 (case 10).—*a*, Posteroanterior view, showing large left hilar mass. *b* and *c*, Angiocardiograms showing mass to be separate from vascular system; lesion proved to be thymoma.

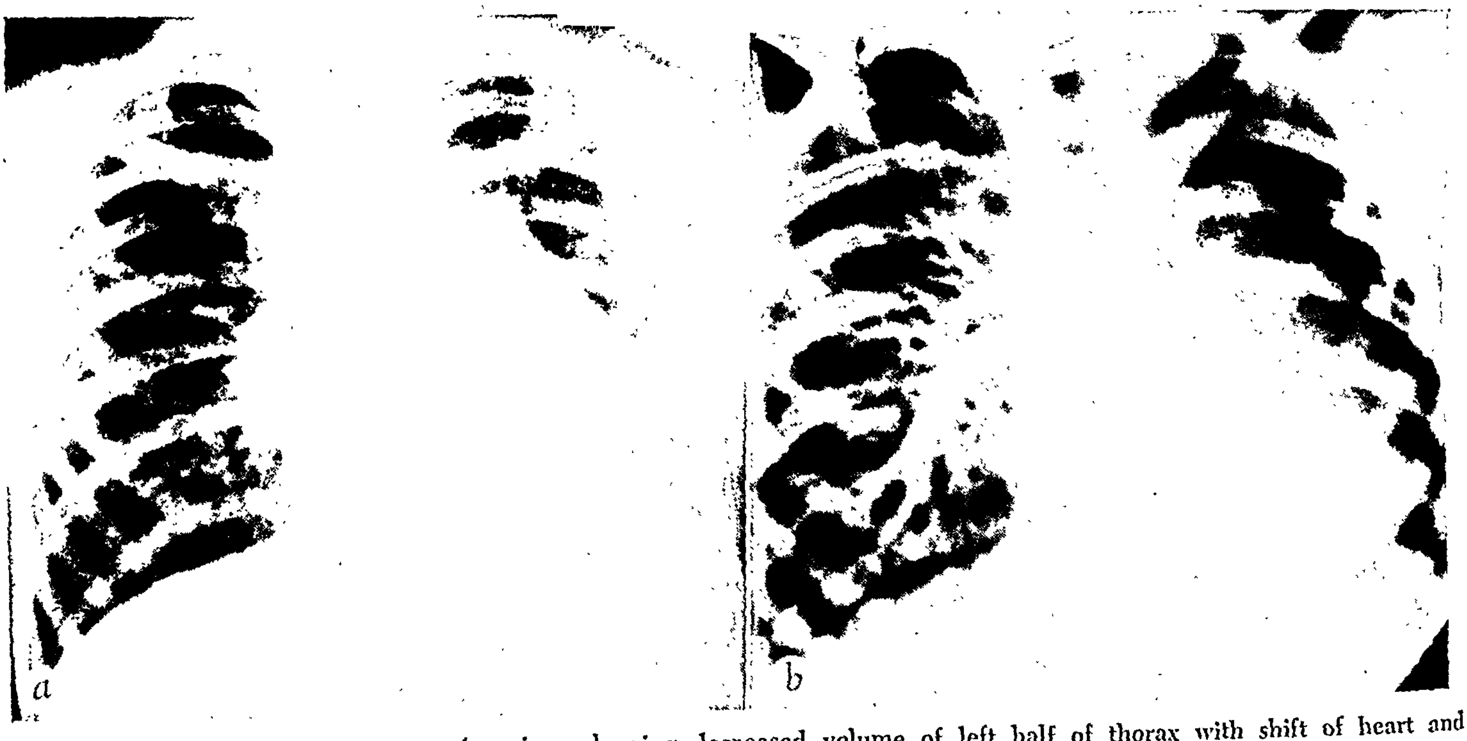

Fig. 11 (case 11).—*a*, Posteroanterior view, showing decreased volume of left half of thorax with shift of heart and mediastinal structures to left. *b*, Selective angiocardiogram with injection into outflow tract of right ventricle, showing absence of pulmonary arterial supply to left lung.

Kinking of the aortic arch is an anomaly which often simulates mediastinal tumor on the posteroanterior thoracic roentgenogram. In some instances the presence of kinking of the aortic arch may be apparent on the left anterior oblique or lateral film of the thorax, but often angiography will be necessary to determine the true nature of the lesion. We have now encountered 11 cases in which kinking of the aortic arch produced misleading roentgenographic signs of mediastinal mass.[4] In several cases, as in case 6, the correct diagnosis was made by angiocardiography or thoracic aortography, and unnecessary mediastinal exploration was avoided.

Case 7.—A 45-year-old woman complained of pain in the back of six to seven years' duration and of progressively severe pain in the left upper part of the abdomen of three months' duration. The results of physical examination were normal. Roentgenographic examination of the thorax revealed the presence of a rounded mass behind the heart on the left side (fig. 7*a*). The result of fluoroscopy was indeterminate. It was thought that the rounded retrocardiac lesion was probably an aneurysm of the lower thoracic aorta.

A thoracic aortogram revealed the thoracic aorta to be normal and the mass to be extravascular (fig. 7*b*). At operation the lesion was found to be a metastatic adenocarcinoma, which was densely adherent to the aortic wall. The primary site was unknown. Palliative x-ray therapy was given after exploration.

Case 8.—A 68-year-old man complained of pain in his back of 30 years' duration which had become worse in recent months. Physical examination revealed some tenderness on percussion over the lower thoracic and upper lumbar portions of the spinal column. The roentgenogram of the thorax showed a rounded mass behind the heart on the left side which did not seem to pulsate at fluoroscopy (fig. 8*a*). It was believed that the mass could be due to either a paraspinal tumor or an aortic aneurysm, and a direct transthoracic aortogram was performed. This showed that the shadow in question was due to neither a tumor nor an aneurysm but only to an exceedingly tortuous but otherwise normal aorta (fig. 8*b*).

Cases 7 and 8 show two entirely different conditions, with exactly the same roentgenographic findings, in which diagnosis of the condition and proper management of the patient were possible because angiography was performed. In case 7 angiography clearly showed the urgent need for exploratory thoracotomy; in the latter patient an unnecessary operation was avoided.

Case 9.—A 52-year-old man with no symptoms was found on routine physical examination to have a loud systolic murmur, maximal over the pulmonic area. A roentgenogram of the thorax showed evidence of a large left hilar mass (fig. 9*a*). This mass was observed to pulsate vigorously, but there was doubt as to whether the pulsation was transmitted or expansile.

An angiocardiogram showed the mass to be due to an extremely enlarged pulmonary artery (fig. 9*b*). The presence of pulmonary stenosis could not be established, and the final diagnosis was idiopathic dilatation of the pulmonary artery. No treatment was indicated. The patient was saved from having unnecessary thoracotomy.

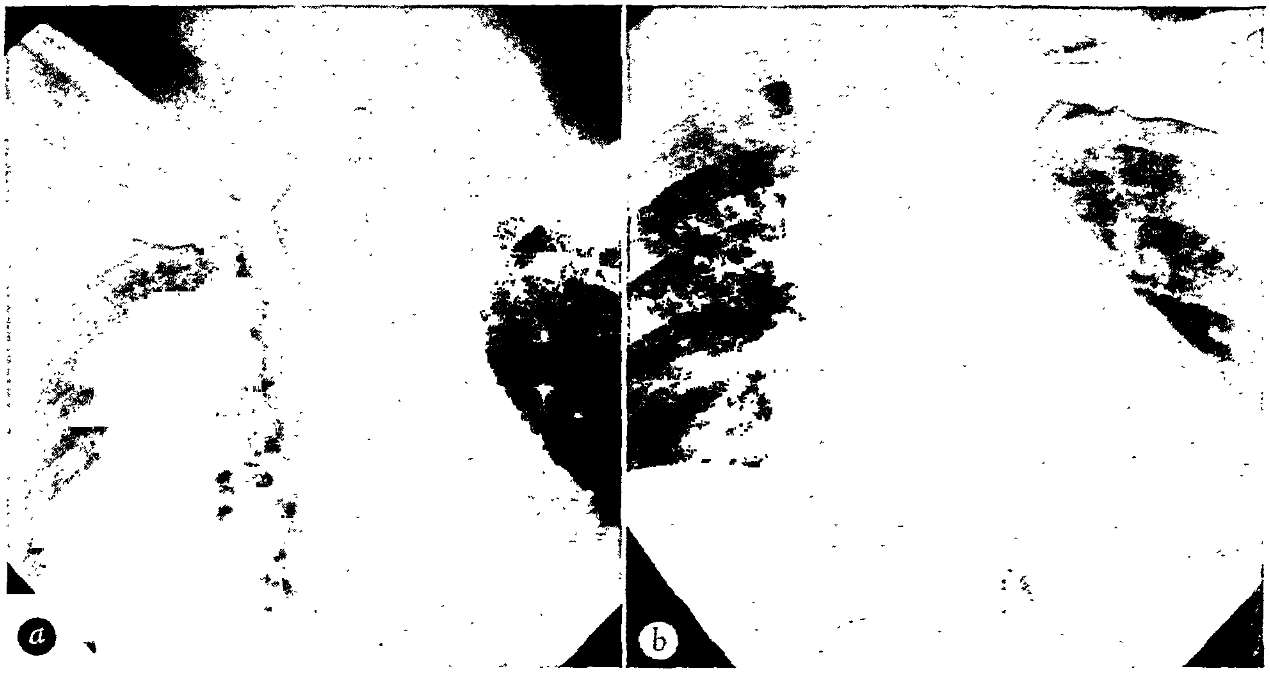

Fig. 12 (case 12).—*a*, Angiocardiogram, showing compression and partial obstruction of superior vena cava by partially calcified mediastinal granuloma. *b*, Postoperative angiocardiogram, after resection of granuloma and replacement of superior vena cava by homologous aortic graft.

Case 10.—A routine roentgenogram of the thorax made by a mobile unit showed evidence of a left hilar mass in a 56-year-old woman. She was told that this was an aneurysm and no treatment was carried out. Six years later she came to the Mayo Clinic with symptoms of progressive fatigability and weakness. Roentgenographic examination at that time again showed evidence of a large mass in the left hilar region (fig. 10*a*). The result of fluoroscopy was indeterminate.

An angiocardiogram proved the mass to be separate from the great vessels (fig. 10*b* and *c*). Thoracotomy was performed, and a biopsy specimen proved the lesion to be a thymoma. The tumor was completely removed. The patient continued to experience fatigue and weakness, but the diagnosis of myasthenia gravis could not be confirmed.

Cases 9 and 10 demonstrate the value of angiocardiography in the differential diagnosis of hilar masses. In our experience, it has been particularly difficult to distinguish vascular lesions from granulomatous and neoplastic lesions of the left hilar region by conventional roentgenologic methods and, in the study of such cases, angiocardiography is performed early in the diagnostic program.[5]

Case 11.—A 5½-year-old boy was known to have had a heart murmur since birth. For three years prior to the time he was brought to the clinic his parents had noted exercise intolerance associated at times with mild cyanosis. Cardiac catheterization indicated the presence of pulmonary stenosis, with coexistent ventricular septal defect and a right-to-left shunt (tetralogy of Fallot). A roentgenogram of the thorax showed evidence of decreased volume of the left half of the thorax and a rather marked shift of the heart and mediastinal structures to the left (fig. 11*a*).

A selective angiocardiogram, with injection through a catheter into the outflow tract of the right ventricle, revealed congenital absence of the left main branch of the pulmonary artery (fig. 11*b*). This condition, which is associated with hypoplasia of the lung on the involved side, accounted for the mediastinal shift and the contraction of the left hemithorax. The angiocardiogram also verified the diagnosis of tetralogy of Fallot, with which congenital absence of the pulmonary artery frequently is associated.

The information supplied by angiocardiography in this case was unobtainable by any other means. [illegible]y revealing the agenesis of the left pulmonary [illegible]ery and thus explaining the unusual appearance of the mediastinum and left hemithorax, angiocardiography played an important role in planning the treatment.

Case 12.—A 41-year-old man complained of progressive swelling of the face and neck of four months' duration. Physical examination revealed, in addition, distention of the veins of the neck and those over the upper anterior portion of the thorax. Venous pressure in the arm was 28 cm. H_2O. These findings indicated obstruction of the superior vena cava.

Roentgenographic examination of the thorax showed evidence of a partially calcified mediastinal mass on the right at the level of the aortic arch. An angiocardiogram revealed compression and incomplete obstruction of the superior vena cava by this mass, which proved to be a mediastinal granuloma completely encompassing the superior vena cava (fig. 12*a*). The granuloma and the involved vessel were resected, and the superior vena cava was replaced by a homologous aortic graft. A postoperative angiocardiogram revealed the graft to be patent (fig. 12*b*).

Angiocardiography is valuable in the study of patients with suspected or known obstruction of the superior vena cava. In addition to establishing the diagnosis, it also will reveal the site of obstruction and frequently the nature and extent of the obstructing lesion, thus serving as a valuable guide in the selection of patients for operation. In case 12 the lesion involved only a short segment of the superior vena cava and it was possible, therefore, to resect the involved portion of this vessel and replace it with a graft. In cases of fibrous mediastinitis or extensive malignant invasion of the superior vena cava, the inoperability of the lesion often will be clearly demonstrated by angiography.

Summary and Conclusions

Angiocardiography and thoracic aortography have been carried out at the Mayo Clinic on 200 patients having a variety of mediastinal lesions. The value of these studies is illustrated by selected clinical examples. Angiographic techniques provide a safe and highly accurate means of distinguishing vascular from nonvascular diseases without thoracotomy and of determining the exact nature, extent, and probable resectability of all vascular lesions of the mediastinum. This latter consideration is of increasing importance today, in view of the recent advances made in the field of vascular surgery. In contrast, fluoroscopy and other diagnostic techniques are inaccurate in distinguishing vascular from certain nonvascular lesions of the mediastinum.

The information provided by angiography, obtainable in no other way, makes it possible in many instances to avoid unnecessary and possibly hazardous mediastinal exploration. In other instances, the necessity of surgical exploration will be clearly indicated and intelligent surgical planning made possible by the use of these techniques.

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POSTOPERATIVE CARE AFTER WHOLE-BODY PERFUSION AND OPEN INTRACARDIAC OPERATIONS

USE OF MAYO-GIBBON PUMP-OXYGENATOR AND BROWNS-EMMONS HEAT EXCHANGER

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Open intracardiac operations, at the present time, can be done with a low risk and a minimum of complications. When complications do occur, they are related primarily to a reduction in cardiac output. Metabolic acidosis or the presence of complete heart block, although rare, can aggravate these states of low cardiac output. To combat such complications when they occur, accurate postoperative care is important. Maintenance of the patient's blood volume at proper levels, treatment of metabolic acidosis when it occurs, and the judicious use of digitalis are the cornerstones of such therapy. In general, every effort should be made to prevent complications by improving the quality and conduct of the operation itself.

The postoperative care of a patient who has undergone adequate whole-body perfusion and open cardiotomy does not differ in any fundamental way from the care exercised after any operation. Primarily because cardiac function temporarily may be suboptimal, greater attention to detail is required. Accurate operative procedures and close observation of the status of the circulation after operation are the keystones of the program.

General Operative and Postoperative Care

A Mayo-Gibbon pump-oxygenator is used at the Mayo Clinic for all perfusions.[1] The incorporation of a Brown-Emmons heat exchanger has made possible complete control of the temperature of the blood. Flow rates of 2.2 to 2.4 liters per square meter of body surface per minute ordinarily are used and have been found adequate to produce nearly normal venous oxygen saturation at normal body temperature.[2]

During operation, the patient's well-being is the responsibility of the anesthesiologist,[3] as well as the surgeon. A detailed, cumulative account of the loss of blood is maintained and serves as the chief guide by which the rate and volume of transfusion are controlled. Administration of fluids is restricted to negligible levels during operation; the total volume of fluids required for administration of the several necessary medicaments and to clear the catheters for physiological measurements is less than 50 ml.

Patients weighing less than 45 kg. (100 lb.) are carefully weighed in the operating room immediately before induction of anesthesia and at the completion of the operation. A scale accurate to 10 Gm. is used. Clamps, stopcocks, bandages, and catheters that are attached to the patient are weighed prior to operation and are meticulously accounted for (see figure).

Postoperative Recovery Unit.—Good facilities and organization are important for ensuring the close attention required by these patients without unduly burdening both professional and nursing personnel. To this end, a postoperative cardiovascular unit into which these patients and others having undergone major cardiac or vascular operations are received directly from the operating room has proved invaluable. Here are concentrated rooms of adequate size, sources of power, properly indoctrinated personnel, complete supplies of all ordinarily used medicaments and the few mechanical and electronic devices of value in such a unit.

Well-motivated nursing and auxiliary personnel are indispensable; their full-time assignment to this unit for extended periods allows them to develop a degree of skill and familiarity that contributes enormously to the smooth functioning of the unit. With their attention, it has not been found necessary to have a physician in constant attendance, although he must be available at all times if needed.

Management of Fluids.—For many reasons, it is advantageous to control carefully the intake of fluids and electrolytes of patients who have undergone whole-body perfusion. The program for administering fluids is based on the assumption that the safest possible course in these patients, who

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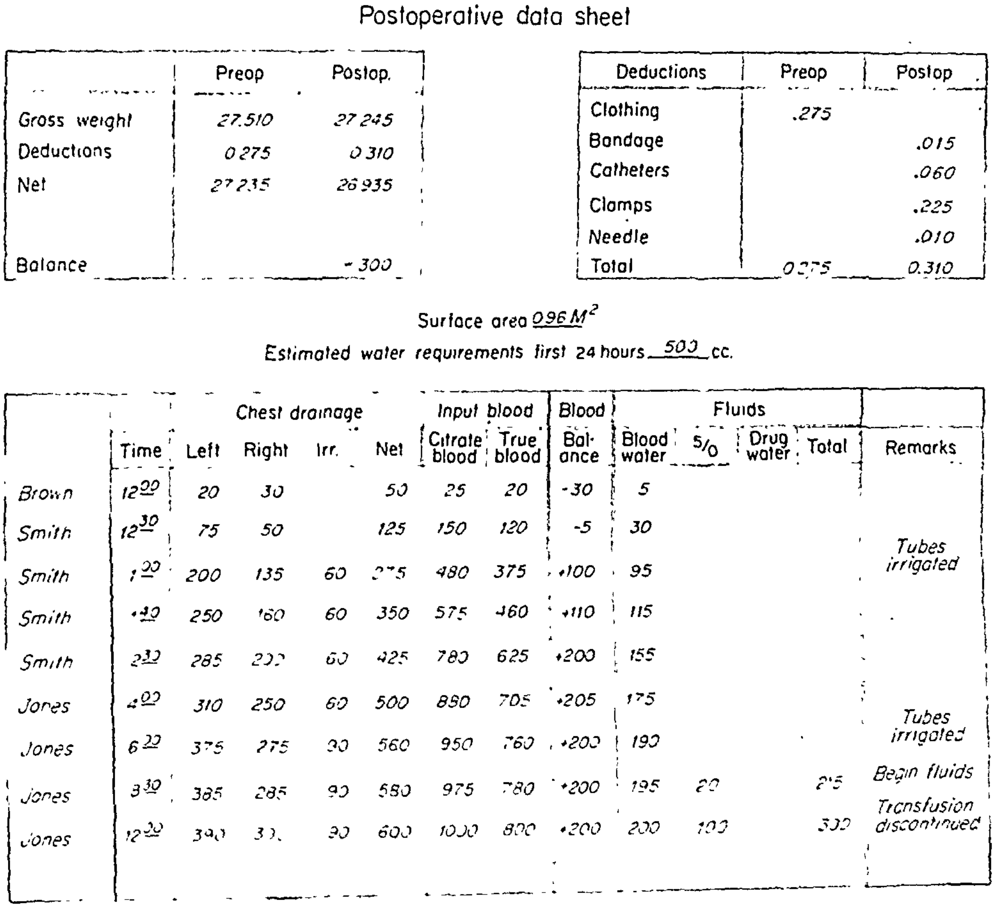
From the Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

may have a suboptimal circulatory status, a severe stress reaction, and depressed renal function, is to provide the least amount of water that, on the one hand, is consistent with physiological requirements and, on the other, will not lead to dehydration. Fluids given over and above insensible losses and the kidneys' excretory ability could result in an undesirable expansion of the extracellular fluid compartment. The prescription of water, then, depends on an accurate knowledge of the rates of net insensible water loss and of obligatory urine water production in patients who are catabolizing rapidly and whose caloric needs are not nearly being met.



Postoperative data sheet

	Preop	Postop.
Gross weight	27.510	27 245
Deductions	0 275	0 310
Net	27 235	26 935
Balance		- 300

Deductions	Preop	Postop
Clothing	.275	
Bandage		.015
Catheters		.060
Clamps		.225
Needle		.010
Total	0 275	0.310

Surface area 0.96 M^2

Estimated water requirements first 24 hours 500 cc.

		Chest drainage				Input blood		Blood	Fluids				
	Time	Left	Right	Irr.	Net	Citrate blood	True blood	Balance	Blood water	5/0	Drug water	Total	Remarks
Brown	12^{00}	20	30		50	25	20	-30	5				
Smith	12^{30}	75	50		125	150	120	-5	30				Tubes irrigated
Smith	1^{00}	200	135	60	275	480	375	+100	95				
Smith	1^{40}	250	160	60	350	575	460	+110	115				
Smith	2^{30}	285	200	60	425	780	625	+200	155				
Jones	4^{00}	310	250	60	500	880	705	+205	175				Tubes irrigated
Jones	6^{00}	375	275	90	560	950	760	+200	190				
Jones	8^{30}	385	285	90	580	975	780	+200	195	20		215	Begin fluids
Jones	12^{00}	390	300	90	600	1000	800	+200	200	100		300	Transfusion discontinued

Postoperative data sheet in use at Mayo Clinic for all patients who have had open cardiotomy and extracorporeal circulation. Illustrative figures are entered for typical patient after correction of partial atrioventricular canal through bilateral anterior thoracotomy. In actual practice, entries would be made much more frequently.

Sturtz and associates[4] studied a number of these tients for the three-day period after whole-body rfusion and open cardiotomy. While the details their study are beyond the scope of this communication, the findings indicate that 500 ml. of water per square meter of body surface on the day of operation and 750 ml. per square meter on the second and third days, when administered at an even hourly rate, will afford a clinically satisfactory state of hydration. In this same study, Sturtz and co-workers found an insensible water loss averaging 400 ml. per square meter of body surface in 24 hours and noted that this figure was about one-half that reported by Heeley and Talbot[5] in a comprehensive study of hospitalized patients. Sturtz and associates thought that, since all their patients were kept in an oxygen tent with two cold-mist dispensers in constant operation, the transpulmonary absorption of water may have affected their figures. It is of interest, however, that their data on insensible water loss agree closely with the water requirements suggested by Schreiner[6] for patients in acute renal failure who likewise have undergone some form of trauma, who are catabolizing rapidly, whose caloric needs are not being met, but who are not exposed to cold-mist dispensers. These sources of information on the rate of insensible water loss have provided the key data on which the program of giving fluids postoperatively is based. The importance of this is emphasized, since these figures differ substantially from the net insensible water loss of persons under basal conditions.

In prescribing a certain amount of fluid for obligatory urine water rather than covering the actual urine water produced, the added advantage is gained that these patients, so many of whom have been in some degree of cardiac failure, may rid themselves of excessive tissue fluid through diuresis on the second or third day after operation. This is a frequent phenomenon despite the small amounts of fluid given. It is admitted that this program is severely restrictive. The margin for error is small but rather on the safe side toward a little dehydration. One must be cognizant of this, and any unusual losses, such as from the gastrointestinal tract, should be promptly and adequately replaced.

Ordinarily, salt is not administered in the three days during which this program is in effect, the needs for fluids being met entirely by the parenteral use of a 5% solution of dextrose in water. It is important that all possible sources of the inadvertent administration of fluids be kept in mind and allowances made accordingly. Especially important in this regard is the postoperative administration of citrated blood. The standard half-liter glass bottle, when filled, contains 480 ml. of blood and 120 ml. of A. C. D. diluent. Therefore, the blood administered is 20% water, for all practical purposes. This fact should be taken into account with respect to both the whole blood administered and the parenterally given fluids prescribed.

Replacement of Blood.—In whole-body perfusion, precise control of the blood volume is important. Likewise, throughout the postoperative period, every effort is bent on knowing exactly the situation with regard to the patient's blood volume. Frequent recording of the balance between blood lost and that replaced is entered on the special postoperative sheet at intervals appropriate to the rate of bleeding. In general, transfusion proceeds at a rate equal to losses from the thorax.

Comparison of the body weight before and after operation is an important guide to the postoperative replacement of blood. In practice, the patient is nearly always deliberately managed so that he weighs less after the operation by an amount that is more or less proportional to his size. It is considered safe to transfuse sufficient blood to restore a patient to his preoperative weight if it appears advisable. However, it should be realized that even this represents overtransfusion to a certain degree, if a left-to-right shunt and a large central blood volume were present before operation. If immediately after operation a patient should weigh 100 or 200 Gm. (3.33 or 6.66 oz.) more than his preoperative weight, losses from the thorax usually are allowed to exceed replacement by this amount gradually over the first few hours in the immediate postoperative period.

Digitalization.—It is desirable for two reasons that the patient undergoing open cardiotomy and extracorporeal circulation not be routinely digitalized before operation. In the first place, the status of digitalization after whole-body perfusion is unknown in the patient previously digitalized; since full digitalization is often desirable in the early postoperative period, it can be fully, rapidly, and confidently achieved when no speculation exists as to how much cardiac glycoside may be in the patient's body. Secondly, the interpretation of postoperative arrhythmias is sufficiently difficult to make desirable the elimination of digitalis as a possible contributing cause of disturbances in rhythm. However, patients who have been receiving digitalis preoperatively because of cardiac failure continue to receive the drug to and through the surgical period.

Digitalization in the early postoperative period is carried out for the usual indications of persistent tachycardia, persistent tachypnea, persistent rales, enlarging liver, evidence of increasing venous pressure, or failure to show a progressive and consistent daily loss in weight. While these signs taken individually may or may not indicate some degree of cardiac failure, nevertheless, any one of them may be considered an early sign of failure and a sufficient cause for digitalization. In addition to these clinical signs, the persistence of a significant degree of right ventricular hypertension after repair is a reason to consider immediate digitalization to combat the possible development of severe reduction in cardiac output. Lanatoside C (Cedilanid) and digoxin are the drugs of choice in this institution. These rapidly acting and rapidly excreted agents are preferred, since full digitalization is desirable in a short period and any untoward effects from some degree of overdosage are of brief duration. The following digitalizing doses are in use: for intravenous use, the calculated dose of lanatoside C is 0.9 mg. per square meter of body surface; for digoxin given intravenously and intramuscularly, the calculated dose is also 0.9 mg. per square meter of body surface. These preparations usually are given fractionally over a short period, the initial dose never exceeding two-thirds of the calculated dose. The calculated dose of digoxin given orally is 1.6 mg. per square meter of body surface, administered in divided doses. Careful clinical and electrocardiographic monitoring of the effects of digitalis is important.

About two-thirds of all patients who have ventricular septal defects or the tetralogy of Fallot are digitalized postoperatively before they leave the hospital. In the latter group, the incidence of temporary late failure of the right side of the heart is sufficiently frequent to make this precaution advisable.

Control of Body Temperature.—Perfusion under normothermic conditions has eliminated the problem of low body temperature at the completion of extracorporeal circulation. However, many patients tend to have sharply increased temperatures in the first few hours after perfusion. Regardless of the cause of this phenomenon, the temperature may be kept readily within reasonable limits if simple measures are instituted early. The rectal temperature is recorded hourly on the day of operation. When the temperature is more than 101.5 F (38.6 C), nurses have standing orders to give 10 to 15 grains of aspirin rectally and to place several ice bags in the bed. The ice bags are removed when the temperature decreases to 100.5 F (38.1 C). A steady condition of the temperature is desirable for many reasons, and these simple measures usually suffice.

Sedation and Analgesia.—While these patients should be alert as soon as possible, restlessness is to be avoided. Morphine sulfate is preferred for all patients regardless of size. It appears to give a maximum of sedation with a minimum of central depression. Remarkably small amounts are effective, the doses ranging from 1/120 grain (0.5 mg.) for infants to 1/20 to 1/12 grain (3 to 5 mg.) for adults. Each dose is given only on the specific direction of the physician.

Feeding.—On the day of operation and for the two next days, no food or water is allowed by mouth, the necessary calories and water being provided entirely by the parenteral route. While this regimen may appear rather stringent, it has been found useful for several reasons. Absolute control of the fluid balance is accomplished; additionally, since gastrointestinal function is often depressed during this period, it eliminates the vomiting and gastric distention that may occur when feeding is started early. Continuous suction via a nasogastric tube rarely is necessary, and adjustments in the fluid and electrolyte program are obviated. With the return of peristalsis, but not before the evening of the third day, oral intake of fluids is permitted and the diet is advanced. Initially, a salt-free (less than 500 mg. of sodium chloride per day for adults and proportionately less for children) diet is prescribed for most patients. If there is no untoward gain in weight on this diet in the subsequent five or six days, the patient receives the so-called low-sodium diet (less than 2,000 mg. of sodium chloride per day for adults and proportionately less for children) before he leaves the hospital. Patients who were in frank cardiac failure before operation and all patients with tetralogy of Fallot continue to take the salt-free diet for about six weeks.

Activities.—Rest in bed for three days is usual for patients after extracorporeal circulation. They are allowed out of bed on the fourth or fifth postoperative day as a general rule. Early ambulation is not forced on these patients, and this rate of progress appears none too slow except for the occasional optimal-risk patient.

Complications

Reduced Cardiac Output.—A reduction in cardiac output after open cardiotomy and extracorporeal circulation, although infrequent, is recognized at this clinic as the most important cause of difficulty in the early postoperative period. In the absence of residual, uncorrected cardiac abnormalities of an important degree, this reduction is a potentially reversible phenomenon and merits prompt recognition and accurate treatment.

A number of investigators have observed this problem both experimentally and clinically. Engell[7] stated that the sharp decrease in pH after perfusion of dogs, especially those with a ventricular incision, probably results from an insufficient output of the heart. Pronounced increases in the arteriovenous oxygen difference and unstable circulatory pressures after perfusion were noted by Davila[8] in dogs. Ito and associates[9] inferred that uncompensated metabolic acidosis after perfusion may be related to inadequate rates of perfusion as well as to periods of reduced cardiac output. In an excellent clinical study, Bahnson and co-workers[10] demonstrated that a seriously reduced cardiac output complicated the postoperative course of a number of patients after cardiopulmonary bypass. They found a close correlation between survival and the adequacy of cardiac output.

The clinical signs indicative of reduced cardiac output in the early postoperative period are familiar to all physicians. They include lethargy or unusual restlessness, low blood pressure, evidence of poor peripheral circulation and a decreasing body temperature. Occasional difficulty with low cardiac output on the operating table may be anticipated, or actually experienced, from certain signs present immediately on discontinuation of extracorporeal circulation. Significant in this regard are sluggish cardiac action (including atrioventricular dissociation), persistent poor color of the heart and surrounding tissues, dark venous bleeding, and the presence of dark blood in the right side of the heart. If, in addition, the systemic blood pressure is low or unstable in the face of accurate restoration of blood volume, it may be assumed that low cardiac output is present.

The possible causes of reduced cardiac output after open cardiotomy and whole-body perfusion have not been identified with certainty. Experience has shown that residual, uncorrected cardiac abnormality of serious degree usually is accompanied by profound circulatory failure. With residual cardiac defects of lesser degree, it is reasonable to suspect that the cardiac output may be proportionately impaired. Particularly important in this connection is the right ventricular hypertension that may persist after closure of a ventricular septal defect complicated by severe pulmonary vascular obstruction or after incomplete correction of the pulmonary stenosis in tetralogy of Fallot. We share the opinion of Barnard and associates[11] that these residual lesions are dangerous to the patient partly because of their contribution to reduced cardiac output in the early postoperative period.

Preoperative cardiac failure may be a predisposing factor by reason of myocardial impairment. The risk of elective cardioplegia, although slight in our experience, probably is related to a subsequent temporary reduction in cardiac output. Stirling and co-workers[12] demonstrated that ventriculotomy in conjunction with perfusion produces a significant impairment of right ventricular function and that this impairment is greater with larger ventriculotomies. Inadequate perfusion may be offered as a cause for reduced cardiac output. However, since there may not be complete agreement as to what constitutes adequate perfusion, it is suggested that perfusion rates that permit the development of appreciable metabolic acidosis may impair cardiac function after operation. The point is that metabolic acidosis, which may be partially compensated up to the time of extubation, will result in a decrease in pH as the carbon dioxide pressure thereafter increases toward normal. That a decrease in pH can impair the action of the heart was demonstrated many years ago by Paterson[13] and more recently by Nahas,[14] who showed experimentally that at a pH of 7.15, for example, cardiac output is reduced 50%.

Specific treatment should be instituted as soon as there is evidence suggesting severe reduction in cardiac output after extracorporeal circulation is discontinued. Low systemic blood pressure, severe reduction or absence of the radial pulse, and peripheral cyanosis and lethargy, occurring in the absence of hypovolemia, suggest that treatment must be directed to the heart. Digitalis should be administered promptly under these circumstances. If an immediate effect on cardiac output is needed, epinephrine is the drug of choice; 1 to 2 ml. of a 1:10,000 solution is given intravenously at first, and the drug is given thereafter as necessary, as a slow continuous drip of 4 mg. in 250 ml. of a 5% solution of dextrose in water. When the signs of reduced cardiac output are persistent, it is our practice to administer a 5% solution of sodium bicarbonate intravenously in a dose of 2 ml. per kilogram of body weight.

The incidence of the syndrome suggesting low cardiac output has diminished steadily as the quality of the operation and the general management of the patient have improved.

Metabolic Acidosis.—Several authors have recognized some degree of metabolic acidosis as a consequence of certain types of whole-body perfusion, the degree of derangement being in general directly proportional to the length of perfusion and inversely proportional to the flow rate. DeWall and associates[15] reported the spontaneous reversal of this state of acidosis within the first few hours after operation. However, Ito and co-workers[9] reported that, in some instances, metabolic acidosis may be progressive and severe during the postoperative period.

Recent studies on a series of clinical perfusions reported from this clinic reveal that at full flows (2.4 liters per square meter per minute) and normal temperature (98.6 F [37.0 C]) a steady state free of metabolic acidosis has been achieved.[2a] These results suggest that the uncompensated metabolic acidosis that may occur several hours after perfusion, and to which Ito and co-workers have called attention, perhaps is caused primarily by a reduced cardiac output.

Heart Block.—While arrhythmias of every description may be seen after open correction of septal defects, the most important one is complete atrioventricular dissociation. As the anatomic relationships of the bundle of His have become better understood, more appropriate placement of sutures has resulted in a sharp reduction in the incidence of this serious complication. When it occurs, however, its proper treatment is essential.

In nearly every case in which complete heart block complicates the postoperative course, the block is apparent at operation. The persistence of dissociation for more than a few minutes calls for the initiation of measures to improve the heartbeat and to provide protection against the ever-present threat of spontaneous asystole. The best method of accomplishing this is by means of electric stimulation begun as soon as the diagnosis of persistent dissociation is made, while the thorax is still open. A braided wire is sewn into the right ventricle according to the method of Weirich and associates[16] and connected to a pacemaker. Thereafter, stimulation is continued for at least 72 hours without an attempt at discontinuation unless, of course, the patient obviously is overriding the pacemaker. Isoproterenol (Isuprel) hydrochloride is given rectally in doses of 2.5 to 5 mg. during the period when discontinuation of stimulation is attempted. This period, during which the patient may be alternately in and out of sinus rhythm, is most critical, and constant vigilance is required lest a brief period of asystole be fatal.

Hemorrhage.—Serious postoperative bleeding has become an uncommon complication of open intracardiac operations. However, on rare occasions bleeding may be considerable. Accurate continuous replacement of blood is essential, and it is in this circumstance particularly that the A. C. D. diluent should be taken into account. A thoroughly adequate drainage system for the thorax, with continuous negative pressure, must be in operation, and the patient should be turned from side to side in order that pleural collections may be aspirated effectively. If some doubt exists on this score and the patient's blood pressure is not satisfactory, repeated thoracic roentgenograms should be taken. It is extremely hazardous to overtransfuse the patient arbitrarily on the grounds that some blood, of an unknown quantity, is present in the thorax.

When postoperative bleeding continues for four or five hours, serious consideration must be given to reoperation. This has been necessary in only three cases in our experience; in each instance, a branch of the right coronary artery that had been cut in making the ventriculotomy was spurting.

Pulmonary Complications.—Our experience indicates that whole-body perfusion and open cardiotomy need not be accompanied by an undue incidence of pulmonary edema or excessive tracheobronchial secretions. Careful control of fluids and replacement of blood during the perfusion and in the postoperative period are important and must be taken for granted. A confined atmosphere heavily laden with cool mist is beneficial in the early postoperative period. However, the prevention of postoperative pulmonary complications is related above all to the quality and technique of perfusion and operation. Factors that may be of importance in this regard are (1) the maintenance of the lungs in a condition of partial expansion during the perfusion by the use of a mixture of 50% helium and 50% oxygen, (2) the careful aspiration of all air from the right ventricle and pulmonary artery before the heart is closed, (3) the prevention of pulmonary congestion caused by trapping of bronchial blood while the bypass is being used, and (4) the technique of perfusion itself. Interstitial pulmonary hemorrhage and its consequences may well be related to the last two factors especially. Should pulmonary complications of sufficient severity occur, tracheotomy and mechanical assistance to ventilation may be used, but these rarely have been required in our experience.

Summary and Conclusions

The program of postoperative care of the patient who has undergone open cardiotomy and extracorporeal circulation is simply an extension of the principles and practices of the operation itself. A sound technique of perfusion, accurate knowledge and control of the blood volume during operation and the postoperative period, and close attention to detail form the basis for a smooth postoperative course. The principal complications are reduced cardiac output, metabolic acidosis, heart block, hemorrhage, and pulmonary difficulties. The most effective management of such complications lies in their prevention. Experience shows that such prevention is possible through efforts directed at improving the quality and conduct of the operation and the perfusion rather than through special efforts taken in anticipation that the complications must occur inevitably.

Credit for establishment of the postoperative cardiovascular unit is due to the Sisters of St. Marys Hospital. The Sisters also set up and staffed this area.

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FATAL CASE OF CONGENITAL PLASMA THROMBOPLASTIN COMPONENT DEFICIENCY

FAILURE OF RESPONSE TO THERAPY IN CHRISTMAS DISEASE

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There is little available information regarding the treatment of plasma thromboplastin component (PTC) deficiency (Christmas disease.) An 18-year-old man with this disease developed a hematoma which increased in size despite multiple whole blood and plasma transfusions. No inhibitors or antibodies against PTC were present, and as much as 3 liters of whole blood was administered in one 24-hour period. Nevertheless, the PTC concentration did not rise to a level higher than that found in the mildest untreated cases of the disease. The patient died in extreme dyspnea, and autopsy revealed an extensive retroperitoneal hematoma, hemoperitoneum, and left hemothorax. The levels of PTC concentration actually attained by the treatment given would be expected if equilibration of PTC between intravascular and extravascular spaces occurs and if the half-life does not exceed 24 hours. The amount of blood or plasma needed to produce a hemostatic level of PTC in the disease is probably equal to that required in classic hemophilia of the same degree of clinical severity.

There is little available information regarding the general treatment of congenital plasma thromboplastin component (PTC) deficiency (also called Christmas disease or hemophilia B) because the opportunities for study of the response of these cases to surgery or major crises such as intra-abdominal bleeding or hematemeses are limited by the rarity of the disease. Biggs and Macfarlane[1] state that such treatment should be easier than in hemophilia since PTC (also called factor 9 or Christmas factor), unlike the antihemophilic (AHF) factor (factor 8), which is deficient in hemophilia. is relatively stable and not used up or consumed during coagulation so that its blood level should thus be more readily raised and maintained by transfusion. Aggeler[2] also states that plasma transfusion is usually more effective in controlling hemorrhage in patients with PTC deficiency than in patients with hemophilia. The following case is reported because it suggests that plasma thromboplastic deficiency is no easier to treat than classic hemophilia of the same clinical degree of severity.

Report of a Case

An 18-year-old man, known to have plasma thromboplastin deficiency, was first seen on Dec. 15, 1958, complaining of severe pain in the left flank. Three days previously while at school he had received a moderately forceful blow in the left flank and several hours later began to have some discomfort in this area and to feel pain on extending the left hip. These symptoms gradually became more severe over the next 48 hours, and on the day prior to examination he had severe pain associated with nausea and vomiting. At this time he began to notice some swelling in the left side of the upper part of the abdomen.

He gave a history of repeated episodes of pain and limitation of movement associated with swelling in the elbow joints, hips, and ankles. All of these episodes occurred after minor trauma. He denied having had epistaxes, bleeding from the alimentary tract, or hematuria. The family history showed a sex-linked recessive pattern. The patient was the youngest of three brothers, who were all affected. The level of PTC, measured by the partial thromboplastin and thromboplastin generation tests, appeared to be the same in all three brothers; nevertheless, the patient's condition was considerably more severe than that of his two brothers.

Examination showed that the patient was a well-developed and robust young man who was obviously in acute distress and unable to lie flat on the table. The left hip was flexed to 90 degrees and could be extended only with extreme pain. The pulse rate was 124 per minute, and the blood pressure was 130/70 mm. Hg. The skin was somewhat pale, and there was some sweating. The abdomen was flat, and there was moderately severe tenderness over

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the entire left side of the abdomen. Bulging in the left flank was noted, and there was extreme tenderness in this area as well as in the left costovertebral angle. All movements of the left hip except extension were painless. The remainder of the joints of the extremities showed no deformity, swelling, stiffness, or other abnormalities.

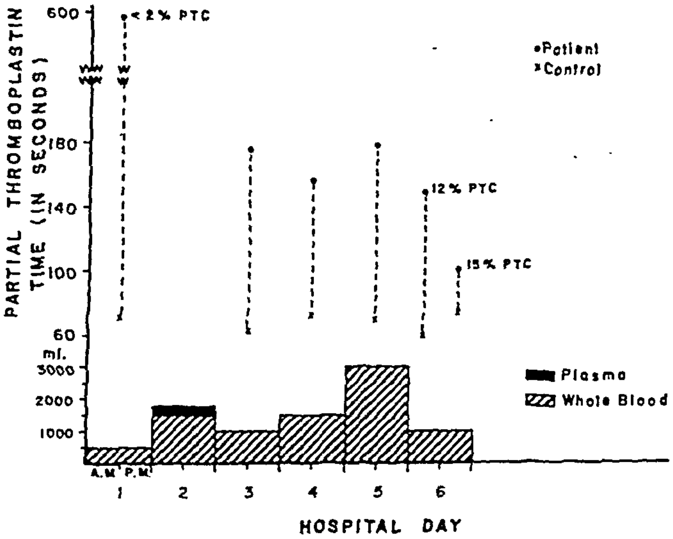
Routine Laboratory Findings.—When the patient was admitted, the hemoglobin level was 13.4 Gm.%. Urinalysis showed negative results. The Lee-White coagulation time was 14 minutes. The next morning the hemoglobin level was 11.8 Gm.%.

Coagulation Studies.—The patient was studied three weeks before he had the illness reported here. The partial thromboplastin time (PTT), tested by the method of Langdell, Wagner, and Brinkhous,[3] was 600 seconds (normal control 70 seconds). The serum was abnormal and the plasma normal in the thromboplastin generation test. The defect was not corrected by the serum of a patient with PTC deficiency. Specific search was made for a circulating anticoagulant with the methods of Dawson[4] and Rodman, Barrow, and Graham,[5] but no such anticoagulant was found. Similar tests for circulating anticoagulants were repeated at intervals during the course of the patient's terminal illness but always showed negative results. Specific PTC tests showed the level of this factor in the patient to be less than 5%. Prothrombin consumption was abnormal; the utilization of AHF and factor 5 was also abnormal.[6] The one-stage prothrombin time was normal. The patient's two brothers have also been studied and found to have the same level of PTC as the patient.

Treatment.—Treatment initially consisted of bed rest and the administration of whole blood and plasma. The patient was given 2,000 ml. of whole blood and 250 ml. of plasma during the first 36 hours of hospitalization. The effect of these transfusions on the PTT is shown in the figure. During this period no increase in the swelling in the left flank was apparent. In general, the patient's condition remained stable, and the blood pressure ranged between 138/90 and 106/76 mm. Hg.

On the third day of hospitalization the hemoglobin level was 8.4 Gm.%. The Lee-White coagulation time was 15 minutes and the PTT 173 seconds (normal control 65 seconds). A definite increase in the size of the left flank mass was then observed, and the clinical picture became complicated by the occurrence of oliguria, cerebral disorientation and irrationality, and an elevation of the blood urea nitrogen level to 65 mg.%. The administration of whole blood and 10% glucose solution in water was continued. Subsequently, the patient had diuresis accompanied by a return to normal cerebral alertness and orientation on the fifth day of hospitalization. The blood urea nitrogen level fell from a high of 110 mg.% to 43 mg.%. During this entire period the blood pressure had been maintained at a stable and normal level. However, the hemoglobin level continued gradually to decrease until 4 p. m. on the fourth day, when a low of 5.4 Gm. was reached. With the institution of a continuous slow intravenous drip of whole blood, the level increased gradually until it reached 11.0 Gm. 48 hours later.

On the sixth and final day of hospitalization the patient first experienced dyspnea. The respirations were shallow and rapid. There were moist rales in the extreme base of the right lung posteriorly, and an area of dulness was percussed over the left base. The left flank was tense. An attempt to aspirate blood from the mass with an abdominal paracentesis trochar was unsuccessful. Shortly thereafter the respirations became extremely labored and the patient died.



Effect of plasma and whole blood transfusions on partial thromboplastin time.

The daily determinations of PTT from the third through the final day of treatment showed no appreciable change until several hours prior to death, when a time of 102 seconds (normal control 75 seconds) was reached (see figure). During the period of treatment 8,500 ml. of whole blood and 250 ml. of plasma were given.

Autopsy Findings.—When the body was opened over 1,500 ml. of unclotted blood was found in the left pleural space, which compressed the left lung into an atelectatic organ. A huge retroperitoneal hematoma of clotted blood was found in the abdominal gutter on the left, overlying and including a shredded mushy left psoas muscle. The hematoma had extended superiorly through the left leaf of the diaphragm. The overlying intestine was elevated by the hematoma, and the mesentery of the intestine was distended with hemorrhage. The left kidney and adrenal gland were surrounded by the hematoma, but their tissues were intact. About 1,000 ml. of unclotted blood was found free in the peritoneal cavity. No bleeding point could be identified, although the muscle and retroperitoneal tissue were converted into a mush that was included in the hematoma. The right lung weighed 750 Gm. and was atelectatic except for a small portion of the upper lobe. The pedicle of the spleen was involved in the retroperitoneal hematoma, which extended medially around the second portion of the duodenum and into the lesser mesentery of the stomach. The kidneys each weighed 175 Gm. and on section presented a normal architecture. No other significant changes were found.

Microscopic studies showed early focal polymorphonuclear cell infiltration into the nonatelectatic areas of pulmonary tissue. Many of the pulmonary alveoli contained pigment-filled macrophages. There was a mild lymphocytic infiltration surrounding the cholangioles of the portal areas in the liver. Sections of the large retroperitoneal hematoma showed lysis of blood cells with polymorphonuclear cell infiltration. Small groups of psoas muscle cells separated by areas of hemorrhage were present. No changes were noted in the sections of the other organs and glands.

In summary, hemothorax on the left; hemoperitoneum; retroperitoneal hematoma and hemorrhages into the diaphragm and left psoas muscle; pulmonary edema; and atelectasis of left lung and right lung were found.

Comment

It has been shown that the PTC concentration of bank blood stored at 4 C remains practically unchanged for three weeks and that little or no loss of PTC occurs when blood is drawn from a donor.[7] Moreover, plasma can be prepared from outdated blood, blood which has been stored 19 to 25 days at 4 C and then stored at −20C without appreciable loss of PTC.[7a] However, plasma stored at room temperature has a low PTC content.[8]

All the blood and plasma given to this patient was less than three weeks old and had been stored at 4 C, so that the PTC content may be considered to have been the same as that of freshly drawn blood or plasma. The patient's blood volume may be roughly calculated from his body weight, which was 117 kg. (257 lb.), to have been 7,500 ml. If it is assumed that the rate of loss of PTC because of equilibration between extravascular and intravascular spaces is negligible and that the rate of utilization of PTC is not increased by tissue damage, then the rapid administration of 3,000 ml. of whole blood would be expected to raise the patient's level of PTC from his initial level of less than 5% to about 40%. As the half-life in vivo of AHF is believed to be 10 to 24 hours and the half-life of PTC is believed to be greater than that of AHF, an estimate of 24 hours would be conservative, as the true figure is probably greater. According to this figure the PTC level would be 20% the day after the transfusion. This amount of blood, 3,000 ml., was given to the patient over a period of several hours on the third hospital day, while a further 1,000 ml. was given the next morning. The PTC level after the administration of all this blood was only 15%, which is a lower level than that which was expected after the administration of 3,000 ml. alone on the previous day; moreover, the additional 1,000 ml. given just prior to testing should theoretically have raised the PTC level at least 10% more. However, it is known that equilibration of AHF occurs between extravascular and intravascular compartments and increased destruction of AHF occurs in the presence of tissue damage.[9] It is, therefore, reasonable to suppose that this is also true in the case of PTC, so that the two assumptions on which the above theoretical calculations were based are probably invalid. This may be the reason for the difference between the theoretical calculated level and the level actually attained. Similar discrepancies have been reported.[10]

Throughout the course of this last hospital admission the patient received at least one unit of blood daily. The actual therapeutic benefits derived from this blood are difficult to evaluate. From the onset of the illness there was severe disrupture and probably necrosis of tissue which resulted in several potential bleeding points. It is possible that bleeding occurred only during the periods when the PTC concentration was at its lower level; if the concentration could have been maintained at a higher level further bleeding into tissues might not have occurred. The hemostatic level of PTC is not known, but some patients who have hemorrhagic manifestations have PTC levels as high as 25% of the mean normal PTC level, so the hemostatic level of this factor must exceed 25% in nonhemophiliacs. It is unlikely that at any time during the course of this patient's illness a hemostatic level of 25% was attained, for even after the intensive course of therapy given on the third and fourth day after admission the level was only 15%. It is, therefore, fair to conclude that despite therapy this patient had an increased tendency to bleed throughout his illness.

To attain and maintain an adequate hemostatic level of PTC of over 25% in a patient with a severe case of PTC deficiency is a formidable procedure. There are some reports of dramatic effects after transfusions of small amounts of blood given because of hemarthroses to patients with hemophilia or PTC deficiency. However, hemarthroses in patients with either hemophilia or PTC deficiency usually resolve without any treatment. Whenever surgery has been performed in patients with hemophilia, large amounts of blood have almost invariably been required and the life of the patient has been in the balance. It is only fair and safe to conclude that this is also true of PTC deficiency.

Summary

A patient with plasma thromboplastic (PTC) deficiency (Christmas disease) had a hematoma in the left flank which, despite administration of large amounts of blood and plasma, extended into the thorax and peritoneal cavity and ultimately caused death. It is generally believed that patients with PTC deficiency need a lesser amount of blood for the control of hemorrhagic episodes than patients with hemophilia. The present case throws considerable doubt on the validity of this belief and suggests that the amounts of blood or plasma necessary to produce a hemostatic effect are the same in the two diseases, provided they are equally severe.

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OSTEOMYELITIS OF THE ILIUM

MASQUERADING AS ACUTE APPENDICITIS.

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The differential diagnosis of abdominal pain includes a number of entities, one of which is acute osteomyelitis of the ilium. Von Bergmann,[1] in 1906, reported 71 instances of osteomyelitis of the pelvis, thus reflecting the relative incidence of this entity. High mortality was noted. Badgley[2] reported 24 cases of acute osteomyelitis of the ilium and emphasized the difficult differential diagnosis. This author noted that typhoid fever and tuberculosis, as well as osteomyelitis of the upper third of the femur, were confused with the malady under consideration. Absence of femoral shaft tenderness and inability to move the hip suggest osteomyelitis of the ilium, whereas position of external rotation and abduction of the hip joint suggest involvement of this articular structure. There is little reference in the literature to the differential diagnosis of acut appendicitis and osteomyelitis of the ilium.

The frequency of involvement of the ilium wa calculated in two series of cases by Badgley. I varied between 1 and 2%. Besa[3] reported an incidence of 0.4% in the year 1947 at the Nationa Orthopedic Hospital in Manila. However, Young, in his review of this entity, estimated that 5% o all cases of osteomyelitis involved the ilium, thi being the flat bone most frequently involved. I is interesting to note that in Young's three case trauma was considered to be an important predis posing factor.

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Sabaino[5] described osteomyelitis of the ilium in a 15-year-old boy who was admitted to the hospital with a history of right lower quadrant pain of two months duration. His clinical condition was critical, and a presumptive diagnosis of periappendiceal abscess was made. The patient was unable to extend his right leg fully. There was tenderness in the right lower quadrant on palpation, and a small tumor was observed over the right ilium. Nausea, fever, and a history of trauma were lacking.

Bruckner[6] described three cases of osteomyelitis of the ilium; two patients had a normal appendix removed because of a mistake in diagnosis. Both patients recovered. The third case was diagnosed correctly, and the ilium was drained satisfactorily. However, 24 hours later, the patient developed a gangrenous appendix. This was judged to be caused by hematogenous spread of the infection to the nearby peritoneum. Leukocytosis, fever, and abdominal pain were present in each patient.

Villeneuve[7] reported a case of acute suppurative osteomyelitis of the iliac crest in a 15-year-old boy, after a fall injury to the involved site. Recovery occurred after surgical drainage. Hizette and Burniat[8] reported a case of osteomyelitis of the right ilium in a 30-year-old woman. This occurred after an abortion and cleared uneventfully after drainage and resection of part of the ilium.

Report of a Case

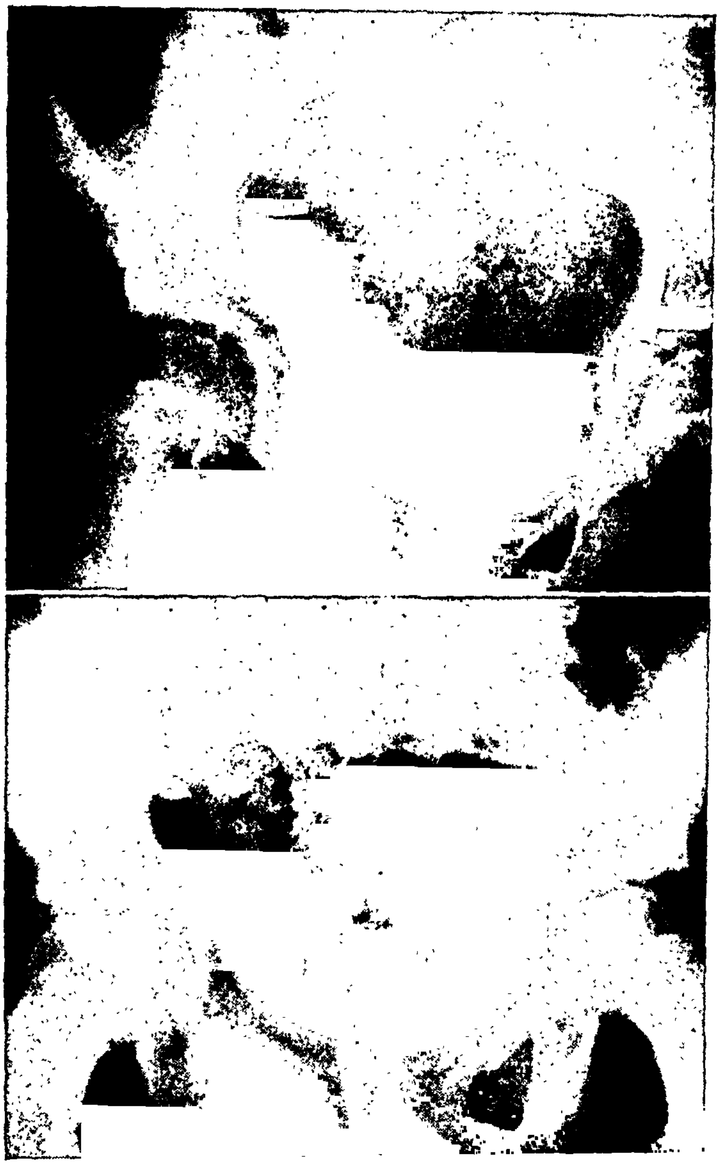
An 11-year-old girl was admitted to Waterbury Hospital, Jan. 20, 1957, with pain of three days duration in the right flank and hip. She had been well until three days prior to admission when she first experienced lower abdominal discomfort and slight pain in the right side of her neck and right hip. These symptoms were attributed to a fall on the ice the previous day. She went to school the next day but was bothered by chills, anorexia, and nausea. The patient had "picked" a facial furuncle just prior to this illness.

The pain in the hip persisted and spread to the right flank. No urinary symptoms were present. Because of fever and persistence of pain in the right hip and flank, she was seen at home, where the only objective physical findings, other than fever, were tenderness of the right flank, minimal discomfort of the right hip when rotated, and tenderness to deep palpation of the right lower quadrant. Urinalysis showed one to eight pus cells per high-power field of the spun sediment. A diagnosis of acute pyelitis was made, and a sulfonamide preparation was given. During the next 24 hours the patient continued to have a moderate fever and to suffer from moderate to severe pain in the right flank and hip. She was hospitalized for further evaluation. Her history was noncontributory except that she had had glandular fever at the age of 7 years. She also had had varicella and rubeola.

Examination after admission indicated a moderately sick child who had a temperature of 104 F (40 C), pulse rate of 120 per minute, and respiration rate of 26 per minute. There was tenderness in the right lower quadrant and over the right flank. No spasm or rebound tenderness were observed. However, tenderness in the right lower quadrant was increased when palpation was performed with the patient in the prone position. In addition, there was slight pain on rotation of the right hip. Urinalysis performed on admission showed only occasional white blood cells and zero to five red blood cells in the sediment. The leukocyte count was 12,200 per cubic millimeter, with 58 segmented forms, 32 stab forms, 5 lymphocytes, and 5 monocytes. The hemoglobin level was 12.3 Gm. per 100 cc. The presumptive diagnoses included acute appendicitis, mesenteric adenitis, acute pyelonephritis, and acute osteomyelitis or septic arthritis of the hip joint. Because of increasing tenderness over the right lower quadrant and an increasing leukocyte count to 15,250 per cubic millimeter, with essentially the same differential count as on admission, the possibility of retrocecal appendicitis was considered, and an appendectomy was performed. At laparotomy, a normal appendix and apparently normal mesenteric lymph nodes were found. After surgery, the patient was given 100 mg. of tetracycline four times daily.

The day after surgery the orthopedic consultant suggested that the disturbance might be in the right hip. There was limitation of hip motion, particularly to abduction and flexion. Pain was elicited in this hip on heel percussion. An attempt to aspirate fluid from the right hip was unsuccessful, but a culture of the procaine penicillin G washings grew Staphylococcus aureus, coagulase negative. This organism was subsequently cultured on one occasion from the blood. During the next few days the patient continued to have a fever; her temperature ranged from 100 to 102 F (37.8 to 39.4 C). Five days after admission, there was tenderness to palpation over the region of the right sacroiliac joint. Motions of the hip which put stress on this joint or compression of the iliac crest resulted in pain. Osteomyelitis of the ilium or sacroiliac joint seemed likely. Tetracycline therapy was discontinued. Penicillin, 2,200,000 units, and novobiocin calcium, 750 mg. per day, were given.

An electrocardiogram failed to show changes consistent with rheumatic fever. A purified protein derivative patch test and agglutinations for typhoid and paratyphoid bacteria, Brucella, Proteus OX19, and infectious mononucleosis gave negative findings. The antistreptolysin titer was 250 units. A roentgenogram of pelvis and hips taken Feb. 15, 1957, three and one-half weeks after admission, established the diagnosis. The right sacroiliac joint (see figure, *top*) appeared fuzzy, and slight periosteal elevation of the adjacent ilium was observed.



Top, periosteal elevation over right ilium denoted by marker. "L" marker over left ilium denotes left side. *Bottom,* sclerosis at site of original osteomyelitis 10 months later.

The remainder of the course in the hospital was uneventful. The antibiotics were changed once again. Therapy with chloramphenicol (1,250 mg. daily) was started on the 14th hospital day and was continued during the hospital stay. Correction of the flexion deformity by traction was started on the 20th hospital day. The temperature fluctuated up to 101 F (38.3 C) orally until 2 days before the patient's discharge on the 34th day. On the day of her discharge the antibiotic was changed to tetracycline, and she continued to take this medicament until April 8, 1957. The remainder of her progress was uneventful. On follow-up examination, one year after the onset of symptoms, orthopedic examination gave completely negative results. Roentgenography at this time showed sclerosis of the ilium at the site of the original involvement (see figure, *bottom*). At the time of this writing, two and one-half years after the original illness, the patient was asymptomatic and had begun to menstruate.

Comment

This case illustrates the difficulty that may be encountered in establishing a diagnosis of osteomyelitis of the ilium during the early acute stages of this malady. Of interest was the presence of pyuria, which suggested acute pyelitis. The increased sensitivity to palpation in right lower quadrant with the patient in the prone position was suggestive of retrocecal appendicitis. The similarity to acute appendicitis was obvious except for the absence of vomiting and abdominal spasm. Also the early pain seemed to originate in the right flank rather than the epigastric region. It should be stressed that although the pain in the right hip was present from the onset, it was not the presenting symptom during the early stage of the illness. Delay in development of definite roentgenographic findings was presumed to be related to use of antibiotics. The facial furuncle and the fall on the ice certainly suggest rather strongly that the origin of the osteomyelitis was the facial infection which spread to the ilium by the hematogenous route.

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APPROACH TO THE ROENTGENOLOGIC DIAGNOSIS OF CONGENITAL HEART DISEASE

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In about 75% of patients with congenital heart disease, the type of malformation present can be accurately determined and its operability predicated by correlation of the history, physical examination, electrocardiographic findings, and conventional roentgenographic and fluoroscopic findings. In the remaining 25%, additional information must be obtained by special methods, such as cardiac catheterization and angiocardiography. Congenital cardiac anomalies can be classified into four groups on the basis of changes in the pulmonary circulation, and certain other criteria afford a basis for further subdivision. A series of roentgenograms illustrates the practical value of these facts.

The widened spectrum of cardiac lesions amenable to surgical treatment has greatly increased the demands for the early and precise diagnosis of congenital malformations of the heart and great vessels. With the accumulation of experience in the diagnosis and treatment of this group of diseases, it has become increasingly apparent that the contribution of diagnostic radiology is a very important one.

Although special techniques such as angiocardiography and aortography are an important part of the radiologist's armamentarium, conventional radiography and fluoroscopy remain the basic diagnostic tools in the roentgenologic examination of the heart. Indeed, it can be said that, with improvement in clinical diagnosis and as a result of lessons learned from the correlation of roentgenographic findings and cardiac catheterization, angiocardiographic, surgical, and necropsy findings the interpretation of conventional roentgenograms has become increasingly important and rewarding.

The purpose of this paper is to discuss some of the capabilities and limitations of the radiologist in the diagnosis of important cardiac malformations and to suggest a useful approach to the analysis of the roentgenologic findings in this group of diseases.

General Considerations

In about 75% of patients with congenital heart disease, the type of malformation present can be accurately determined and its operability predicated by correlation of the history, physical examination, electrocardiographic findings, and conventional roentgenographic and fluoroscopic findings. In the remaining 25%, additional information must be obtained by special methods such as cardiac catheterization and angiocardiographic examination.

The question is often asked, "How much can conventional roentgenography contribute to the diagnosis of congenital heart disease?" It is difficult to answer this question specifically. Bing has stated that "roentgenographic examination constitutes the most important part of the clinical examination in congenital heart disease." This statement, not by a radiologist, but by one who has made important contributions to the knowledge of cardiac physiology, constitutes an unbiased and authoritative opinion of the potential importance of the roentgenologic examination. It should be unnecessary to say that the extent to which this potential is realized is dependent on the radiologist's knowledge of the basic pathological, clinical, and physiological aspects of congenital heart disease and his ability to integrate this knowledge with the roentgenologic findings in a given case. It cannot be sufficiently emphasized that the roentgenologic examination is only one important link in the chain of methods available for investigation of the cardiovascular system, and that only by use of all modes of study is it possible to accurately assess the anatomic and functional state of the heart.

In further answer to this question it might be stated that the roentgenologist's contribution, though an important one, is variable from case to case; that is, in some conditions, such as coarctation of the aorta or the figure-of-eight type of total anomalous pulmonary venous connection, the radiologist can often make a correct diagnosis on the basis of the posteroanterior roentgenogram of the thorax, and his contribution in such instances is large. On the other hand, his contribution to the diagnosis of more complex anomalies is much smaller, unless special methods of investigation, such as angiocardiography, are used. Thus, there are few times when the roentgenologic findings are characteristic of a specific anomaly, but

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there are many occasions when the radiologist can narrow the diagnosis down to a few specific possibilities and, by correlating the roentgenologic features with the clinical findings, can suggest which of these several possibilities is most likely.

For example, when the pulmonary vessels show engorgement of a certain type, several possibilities exist. If it is known that the patient is not cyanotic, the possibilities become fewer and the presence of a left-to-right shunt is almost certain. If, in addition, the aortic knob is large and at fluoroscopic examination the pulsations of the pulmonary arteries are not appreciably accentuated, the chances favor the presence of a patent ductus arteriosus. If, however, the aortic knob is small and the hilar pulsations are markedly increased, the chances favor an intracardiac shunt rather than a patent ductus.

As illustrated by this example, what is important, if the roentgenologic examination is to achieve its maximal usefulness, is for the radiologist to note on the roentgenogram and at fluoroscopic examination certain pertinent features which may serve as useful building blocks in the completion of the final diagnostic structure. These pertinent features are the general cardiac configuration; the heart size (as estimated by the cardiothoracic ratio); the size of the individual heart chambers, when it is possible to determine this; the appearance of the main pulmonary artery and its central and peripheral branches; the size and configuration of the aortic arch; and the presence or absence of rib notching. While it is important to note systematically all these features in each case of suspected congenital heart disease, probably the most important single feature is the appearance of the pulmonary vessels. Not only do changes in the pulmonary circulation accurately reflect the functional pathology of the heart, but the interrelationship is reciprocal in that changes in the pulmonary vessels may play a significant role in determining the behavior of the heart. Much information with regard to pulmonary-artery flow, pulmonary-artery pressure, and pulmonary vascular resistance may be reflected in the roentgenographic appearance of the pulmonary vessels. This information is of extreme practical importance, not only from a diagnostic standpoint, but also from the standpoint of evaluation of the patient as a candidate for operation.

Classification

There are several ways of classifying congenital heart diseases. The pathologist classifies them on the basis of embryologic and anatomic features; the cardiologist usually classifies them into cyanotic and acyanotic groups; and the surgeon usually does not classify them at all, because to him each anomaly is a separate and different therapeutic problem. While there is merit in all these methods of classification, or in not making a classification, no one of them is entirely satisfactory to the radiologist. Knowledge of the presence or absence of cyanosis is, of course, extremely important, for the presence of cyanosis in congenital anomalies, except in terminal heart failure, is usually evidence of a right-to-left shunt. Although the classification of congenital malformations into cyanotic and acyanotic groups is logical, it must be remembered that patients with anomalies characterized by left-to-right shunt and classified in the acyanotic group may, under certain conditions, develop cyanosis. Furthermore, cyanosis is not a roentgenologic finding, and the radiologist when interpreting roentgenograms may not have information regarding its presence or absence.

Classification of Important Congenital Heart Lesions

Increased pulmonary arterial vascularity (increased flow)
  Ventricular septal defect
  Atrial septal defect
  Patent ductus arteriosus
  Persistent common atrioventricular canal
  Anomalous pulmonary venous connection
  Aortopulmonary window
  Transposition of great vessels*
  Truncus arteriosus*
Decreased pulmonary arterial vascularity (decreased flow)
  Tetralogy of Fallot
  Pulmonary stenosis with intact ventricular septum
  Tricuspid atresia
  Ebstein's malformation
  Pseudotruncus arteriosus
  Agenesis of a main branch of pulmonary artery
Normal pulmonary arterial vascularity (normal flow)
  Coarctation of aorta
  Congenital aortic stenosis
Pulmonary venous hypertension (obstruction to pulmonary venous flow)
  Left heart failure from any cause
  Congenital mitral stenosis
  Congenital stenosis of pulmonary veins

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*Increased pulmonary vascularity but with flat or concave pulmonary-artery segment.

A classification has therefore been devised which, from the findings on the conventional roentgenogram of the thorax, permits the radiologist to place the patient in one of four broad diagnostic groups (see table). This classification is based on changes in the lesser circulation. Thus, patients with congenital heart disease are divided into three groups, depending on whether there is increased, decreased, or normal pulmonary arterial vascularity. The term "pulmonary arterial vascularity" is synonymous with pulmonary arterial flow. Increased pulmonary vascularity, and therefore increased flow, is seen in patients with left-to-right shunt. Decreased pulmonary vascularity, or decreased flow, is seen in patients with obstruction to pulmonary arterial flow and right-to-left shunt. Normal pulmonary vascularity is, in general, seen in a miscellaneous group of malformations in which there is no direct communication between the systemic and lesser circulations and, therefore, no shunt or admixture of arterial and venous blood. A fourth group to be considered consists of congenital lesions producing pulmonary venous hypertension owing to obstruction of pulmonary venous flow.

Although this suggested classification shares some of the weaknesses of that based on the presence or absence of cyanosis, it would seem a more logical approach from the standpoint of roentgenographic interpretation.

Conditions Characterized by Increased Pulmonary Arterial Vascularity (Increased Flow)

In the group of conditions characterized by increased pulmonary vascularity, a number of cardiac anomalies must be considered. In all these anomalies there is functionally a left-to-right shunt, either intracardiac or extracardiac, and increased pulmonary-artery flow.

Five Most Common Anomalies.—The most common anomalies in this group are ventricular septal defect, atrial septal defect, patent ductus arteriosus, persistent common atrioventricular canal, and anomalous pulmonary venous connection. These five conditions with left-to-right shunt make up more than 50% of all cases of congenital heart disease. Also included in this group are a number of rarer anomalies such as aortopulmonary window, transposition of the great vessels, and truncus arteriosus.

The chief roentgenographic characteristic of all the malformations in this group with left-to-right shunt, with the exception of transposition of the great vessels and truncus arteriosus, is increase in the size of the main pulmonary artery and its central and peripheral branches, as evidence of increased pulmonary-artery flow (fig. 1*a*). In transposition and truncus arteriosus, the findings are somewhat different, although there is usually increased pulmonary arterial vascularity in these two anomalies also.

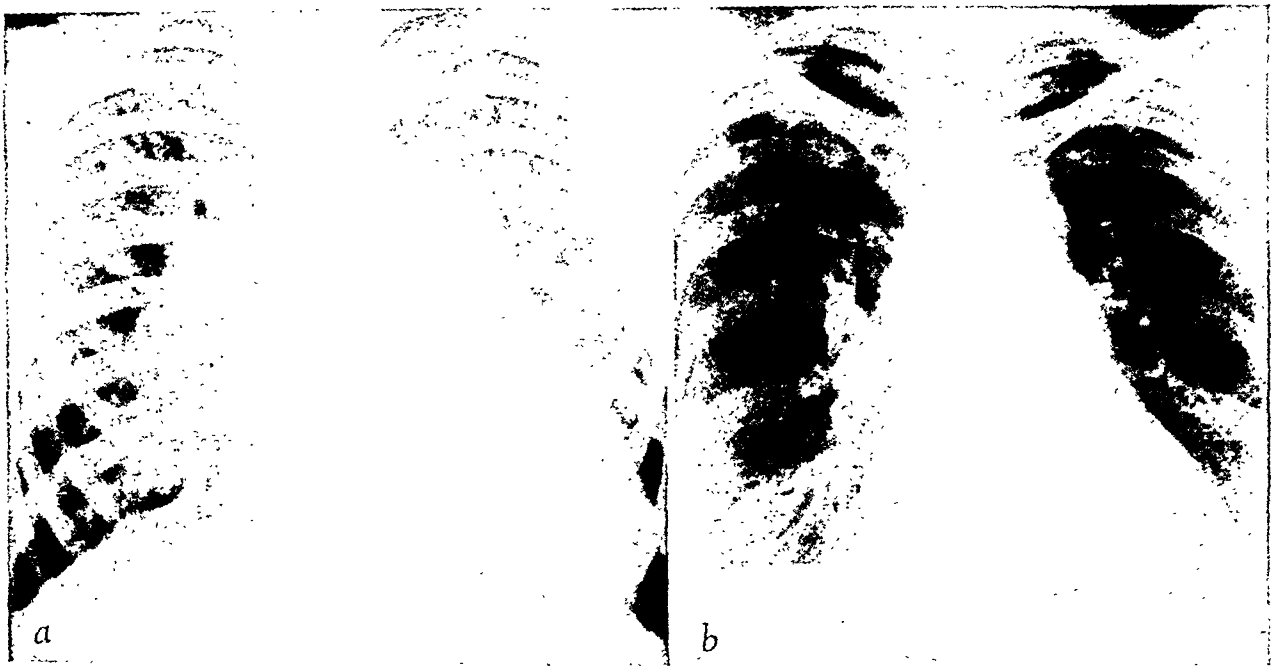

Fig. 1.—*a*, ventricular septal defect, with enlargement of pulmonary artery and its central and peripheral branches as evidence of increased pulmonary arterial flow. Heart is enlarged, and aortic knob appears small. Pulmonary artery and its hilar branches pulsated vigorously at fluoroscopic examination. *b*, patent ductus arteriosus: Aortic knob is bulbous. Pulmonary arteries show evidence of increased pulmonary arterial flow, but at fluoroscopic examination they showed only slightly increased pulsations. Heart is enlarged.

There are no distinct roentgenologic differences between ventricular septal defect, atrial septal defect, and persistent common atrioventricular canal. In addition to increased pulmonary vascularity, all three of these conditions are commonly associated with a hypoplastic aortic knob and vigorous pulsation of the pulmonary arteries as seen fluoroscopically.

Patent ductus arteriosus, however, produces a somewhat different picture in that the aortic knob is usually normal and frequently bulbous in appearance, and the central pulmonary arteries are often less enlarged and at fluoroscopic examination are seen to pulsate less vigorously than in patients with intracardiac shunts (fig. 1*b*). This lesser pulsation is due to the fact that the flow of blood from the systemic to the pulmonary circulation occurs continuously in patent ductus whereas in the intracardiac shunts the flow occurs intermittently. In about 50% of cases, the radiologist is able to distinguish between patent ductus and other lesions with left-to-right shunt on the basis of these differentiating features.

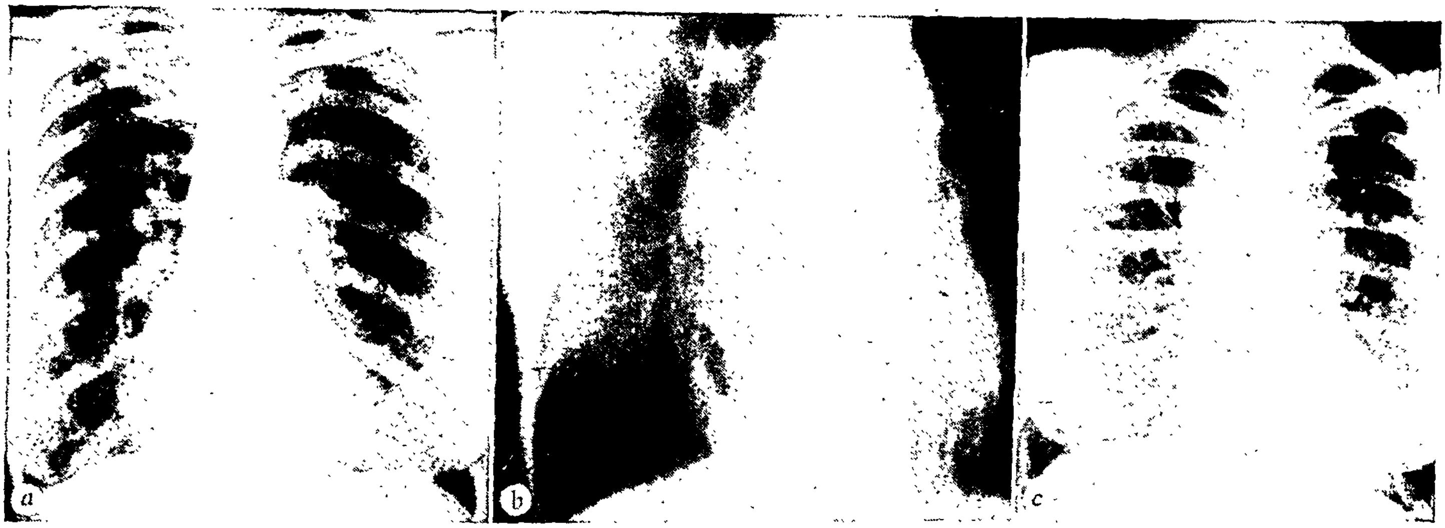

Fig. 2.—Anomalous pulmonary venous connection: *a*, anomalous drainage of right lung into inferior vena cava. Posteroanterior roentgenogram showing anomalous vein coursing along right border of heart. *b*, tomogram of this area demonstrating anomalous vein and its major tributaries from various segments of right lung. c, posteroanterior roentgenogram in case of total anomalous pulmonary venous connection. All pulmonary veins drain into a persistent left superior vena cava. Prominent left and right superior venae cavae superiorly and heart inferiorly produce so-called figure-of-eight conformation pathognomonic of this type of anomalous venous connection. Pulmonary vascularity is increased.

My colleagues and I have found estimation of ventricular enlargement and left atrial size to be of little practical help in differentiating between the various defects associated with left-to-right shunt.

In anomalous pulmonary venous connection one or more of the pulmonary veins, instead of draining normally into the left atrium, drain anomalously into either the right atrium, the superior vena cava, the inferior vena cava, or a persistent left superior vena cava. It has been said that this condition is functionally significant only when 50% or more of the pulmonary venous return drains anomalously. In such instances, cyanosis is usually present.

The pulmonary vascular changes in anomalous pulmonary venous connection vary greatly, depending on the number of pulmonary segments involved. This anomaly is often present without evidence of the anomalous vein or veins on the roentgenogram. In most cases, the only roentgenographic abnormality is prominence of the central and peripheral pulmonary arteries due to the pulmonary recirculation that occurs. In these cases, it is impossible by conventional roentgenologic methods to differentiate anomalous pulmonary venous connection from the other anomalies characterized by left-to-right shunt.

There are, however, two uncommon types of anomalous pulmonary venous connection that may be specifically diagnosed by the roentgenologist. The first is one in which all or part of the right lung drains anomalously into the inferior vena cava at, or below, the level of the diaphragm. In such cases, the anomalous vein may be seen coursing along the right cardiac border (fig. 2*a*). When this anomaly is suspected from the appearance of the roentgenogram, tomography (body section roentgenography) can often be helpful in more clearly defining the anomalous vein (fig. 2*b*). In the other type, there is total anomalous pulmonary venous connection, and the veins from both lungs drain into a persistent left superior vena cava. The striking and characteristic feature of this anomaly is the so-called figure-of-eight conformation, with the heart forming the lower half of the "eight" and the large left and right superior venae cavae forming the upper half (fig. 2*c*).

As mentioned earlier, the radiographic findings in patients with congenital heart disease are important not only from a diagnostic standpoint but also from the standpoint of evaluation of operability. Cardiologists and cardiac surgeons at the Mayo Clinic place a great deal of importance on the radiographic findings in the evaluation of patients for surgical treatment. One reason why the early diagnosis of cardiac malformations is important is that, in patients with large left-to-right shunts, obliterative changes eventually occur in the smaller pulmonary arteries and arterioles which may increase peripheral pulmonary vascular resistance to the point where little or no left-to-right shunt occurs. As these changes in the small peripheral arteries progress, the shunt becomes bidirectional and may become predominantly right to left, and cyanosis may then develop. These changes in the small pulmonary arteries occur most commonly in ventricular septal defect, since in this condition the pulmonary arteries are functionally in direct communication with the left ventricle, a high-pressure chamber. Such changes may also occur, however, in patent ductus arteriosus or, less frequently, in other conditions in which there is a large left-to-right shunt. This particular situation is known as the Eisenmenger syndrome. Patients in whom this increased-resistance type of pulmonary hypertension has developed are not benefited by surgical closure of the defect, and operation may actually be disastrous. This is due to the fact that the changes in the small pulmonary vessels, when sufficiently advanced, may be irreversible. When the defect is closed in these patients, pressure in the pulmonary trunk remains elevated owing to the increased resistance present in the pulmonary vascular bed, and the entire work load of maintaining the pulmonary circulation is placed on the right ventricle, which may then fail.

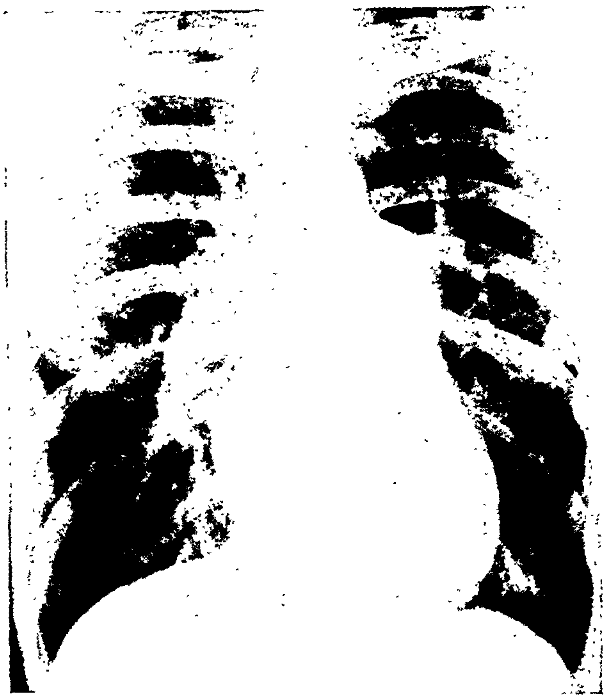

Fig. 3.—Atrial septal defect with obliterative changes in small peripheral pulmonary arteries and increased pulmonary vascular resistance. Pressure in pulmonary artery was equal to systemic pressure. Shunt had become bidirectional, and pulmonary arterial flow was increased but little. Pulmonary artery and its central branches are markedly enlarged, but peripheral pulmonary vasculature is normal or perhaps diminished from normal.

The presence of this increased-resistance type of pulmonary hypertension may be readily recognized on the posteroanterior roentgenogram of the thorax. In defects with a large left-to-right shunt, the pulmonary vessels are enlarged all the way out to the periphery of the lung. In patients who have developed increased peripheral pulmonary resistance due to intimal changes in the smaller pulmonary arteries, the peripheral vessels are seen to be narrowed or normal in size while the central pulmonary arteries are enlarged (fig. 3). Thus, the roentgenographic recognition of the Eisenmenger syndrome is based on the presence of enlargement of the central pulmonary vessels and disproportionate narrowing or tapering of the peripheral pulmonary vessels.

Rarer Anomalies.—Two other anomalies are occasionally encountered which frequently are characterized by increased pulmonary vascularity due to increased pulmonary-artery flow but have roentgenographic features distinctly different from the conditions just discussed. These are transposition of the great vessels and persistent truncus arteriosus.

There are several varieties of transposition of the great vessels (complete transposition, Taussig-Bing syndrome, and corrected transposition), and in most instances there is an associated ventricular septal defect. Increased pulmonary vascularity is an inconstant finding, and, when it is present, the pulmonary-artery segment is flat or concave, rather than prominent. This feature of the pulmonary-artery segment is due to the malposition of the great vessels. In all types of transposition the aorta lies anterior to the pulmonary artery, and, because of this abnormal relationship, the supracardiac vascular pedicle may appear abnormally narrow in the posteroanterior view (fig. 4*a*). In some cases of transposition the ascending aorta may be seen arising on the left rather than in the midline or in its normal position on the right side (fig. 4*b*). The pulmonary artery arises more in the midline than is normal and often can be seen through the shadow of the ascending aorta. Rarely, in instances of transposition of the great vessels, the pulmonary artery, because of its abnormal midline position, can be seen to indent the barium-filled esophagus on the left. Angiocardiography is usually necessary to make a definite diagnosis of transposition and to distinguish the various types of this anomaly.

In persistent truncus arteriosus the pulmonary artery does not arise in normal fashion from the right ventricle, but instead, the right and left pulmonary arteries arise from a large common trunk. This anomaly frequently can be recognized on the posteroanterior roentgenogram (fig. 5). Whenever the aortic shadow appears wider than normal and the pulmonary arteries are prominent and do not appear to have a normal connection with the outflow tract of the right ventricle via a pulmonary trunk, the presence of persistent truncus arteriosus should be strongly suspected. In this condition, as in transposition of the great vessels, the pulmonary-artery segment is flat or concave, a finding of great importance in differentiating these from the other anomalies with increased pulmonary vascularity.

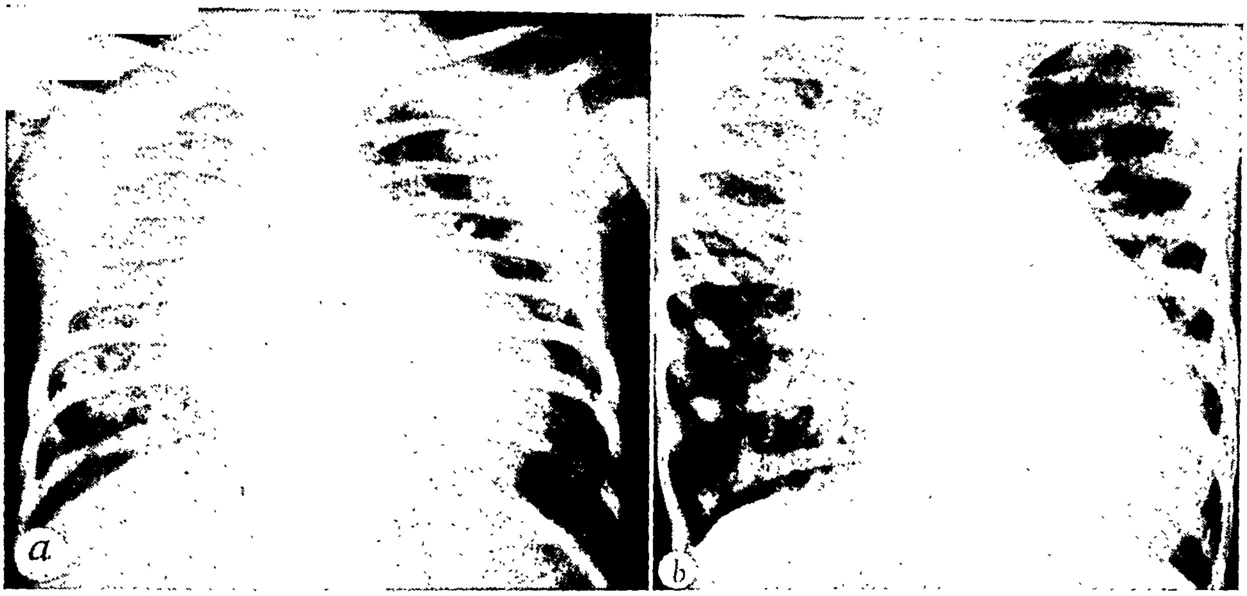

Fig. 4.—Transposition of great vessels: *a*, complete transposition with ventricular septal defect: Supracardiac vascular pedicle is narrow. Although pulmonary vascularity is increased, pulmonary-artery segment is flat. Heart is enlarged. *b*, so-called corrected transposition, with associated ventricular septal defect: Ascending aorta arises on left and overlies left hilus. Pulmonary artery lies more in midline than normal and may be seen through shadow of ascending aorta. Pulmonary vascularity is increased, and heart is enlarged.

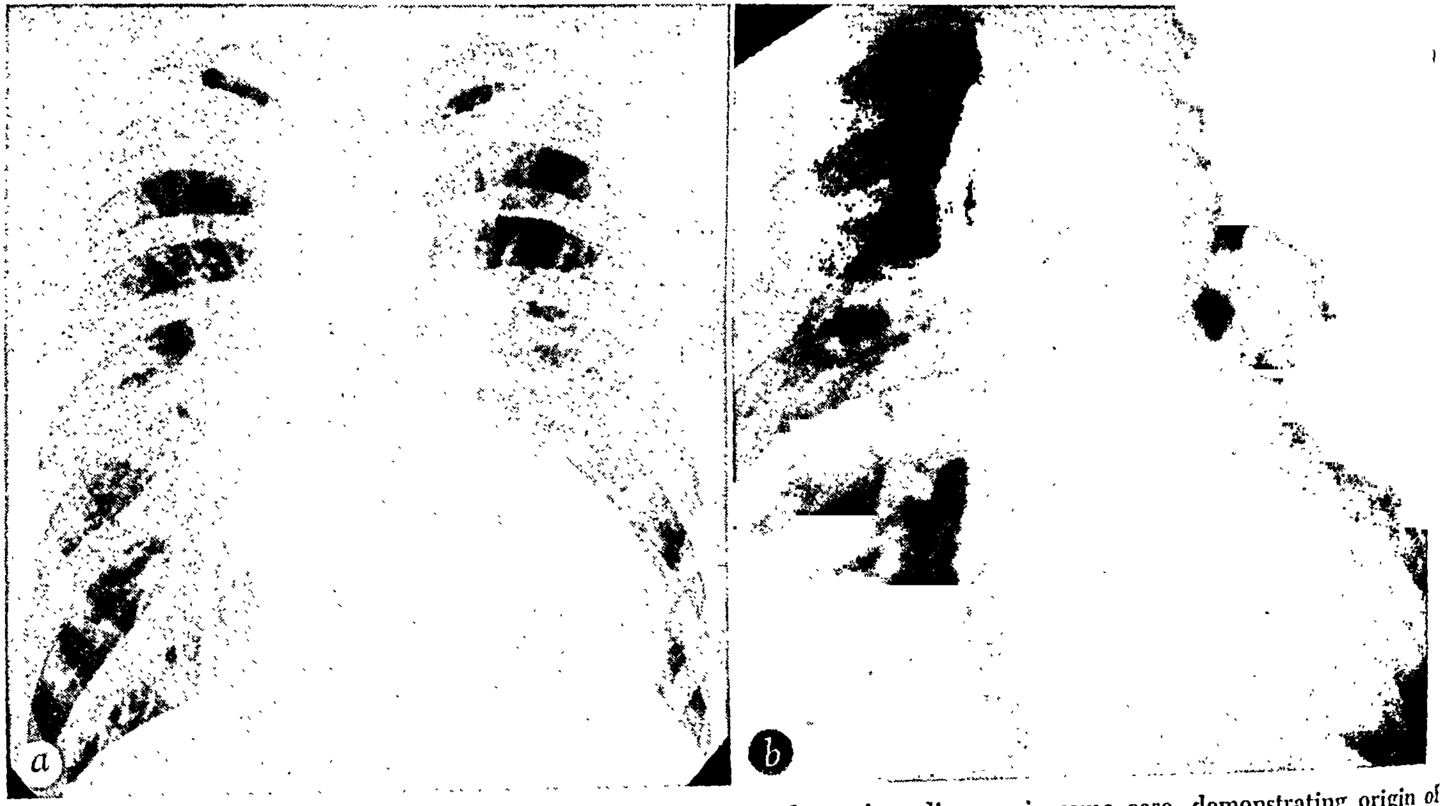

Fig. 5.—Truncus arteriosus: *a*, posteroanterior roentgenogram. *b*, angiocardiogram in same case, demonstrating origin of right and left pulmonary arteries from truncus.

Conditions Characterized by Decreased Pulmonary Vascularity (Decreased Flow)

Decreased pulmonary arterial vascularity is seen in patients who have obstruction to pulmonary arterial flow. This obstruction may be either at the pulmonary outflow tract of the right ventricle or at the tricuspid valve. In certain rare instances, it may be in the pulmonary artery itself or one of its main branches. Most lesions in this group are associated with a right-to-left shunt through a septal defect, and the patient is cyanotic. It is in this group of anomalies that angiocardiography is most valuable.

The most common lesion in this group is pulmonary stenosis with ventricular septal defect, or so-called tetralogy of Fallot. Less commonly seen are cases of pulmonary stenosis with intact ventricular septum, tricuspid atresia, Ebstein's malformation of the tricuspid valve, pseudotruncus arteriosus, and agenesis of a main branch of the pulmonary artery.

Tetralogy of Fallot.—Figure 6*a* shows the findings usually described as being characteristic of tetralogy of Fallot; namely, so-called coeur-en-sabot configuration with elevation of the cardiac apex, clear lung fields with flat or concave pulmonary-artery segment, and right-sided aortic arch. The bizarre appearance of the vessels present in the lung fields is due to a large collateral flow through the bronchial arteries. These dilated bronchial arteries are easily recognized as short vessels which run in a random, disorderly fashion and do not taper as do pulmonary arteries. Unfortunately, from a diagnostic standpoint, the roentgenographic manifestations of tetralogy of Fallot are variable, because the degree of pulmonary stenosis is variable, and this so-called typical picture is seen in only about 20% of cases. In most cases of tetralogy the pulmonary vascularity appears normal, and in a small percentage it may even be increased. This increased vascularity is usually slight, however, and occurs in those patients with so-called pink tetralogy who have only mild pulmonary stenosis, a left-to-right shunt, and no cyanosis. A right-sided aortic arch is more commonly associated with tetralogy than with other cardiac anomalies, being present in about 25% of cases.

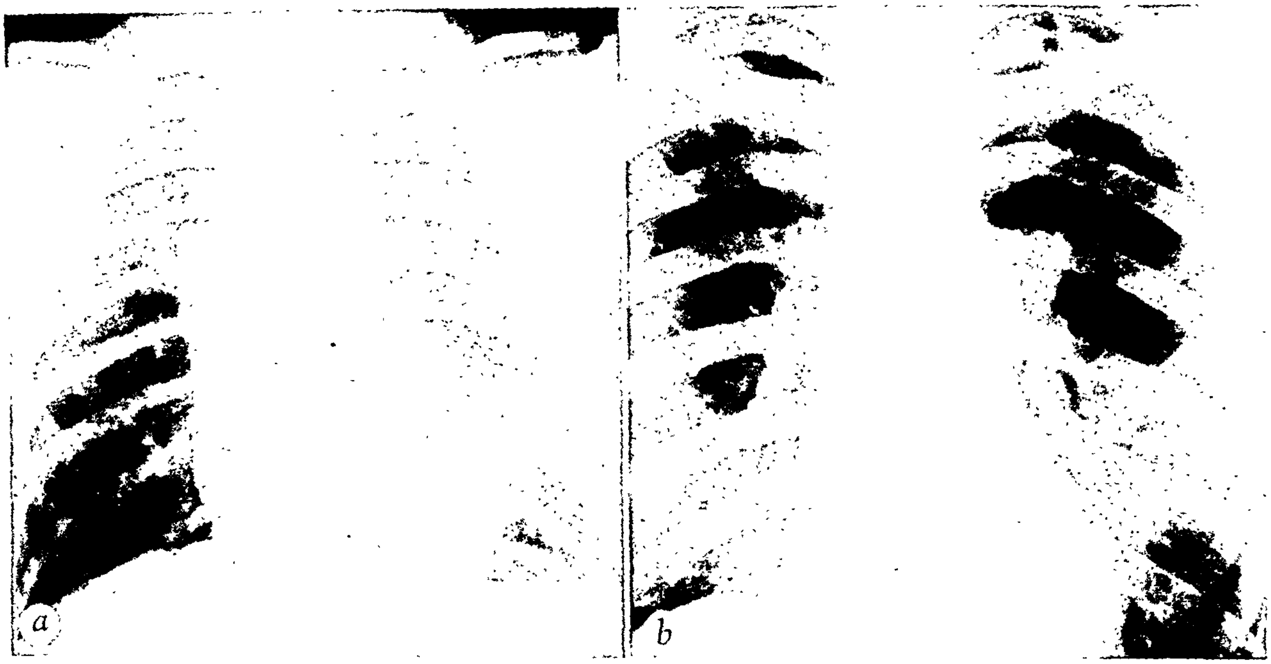

Fig. 6.—*a*, tetralogy of Fallot showing coeur-en-sabot configuration: Pulmonary-artery segment is concave. Right aortic arch is evident. Pulmonary vascularity is diminished. Dilated bronchial arteries are visible in both lungs. This "typical" picture is seen in only about 20% of cases of tetralogy. *b*, pulmonary stenosis with intact septum, showing poststenotic dilatation of pulmonary artery and its left main branch.

Pulmonary Stenosis with Intact Ventricular Septum.—Pulmonary stenosis with intact ventricular septum, often referred to as isolated pulmonary stenosis or pulmonary stenosis with normal aortic root, is a much rarer anomaly than tetralogy. In about one-half the cases of pulmonary stenosis with intact ventricular septum, an atrial septal defect or a patent foramen ovale is present. This particular combination of anomalies is often referred to as the trilogy of Fallot. If the pulmonary stenosis is severe enough in such cases, the elevated right ventricular and right atrial pressures will produce a right-to-left interatrial shunt, with resultant cyanosis. The pulmonary stenosis is almost always valvular, rather than infundibular as it is in tetralogy, although hypertrophy of the right ventricular outflow tract with significant infundibular stenosis is frequently present as well.

Pulmonary stenosis with intact ventricular septum presents fairly consistent and characteristic findings on the plain roentgenograms, which permit the radiologist to suggest the correct diagnosis in a relatively high percentage of cases. Poststenotic dilatation of the pulmonary artery is a classic roentgenographic finding in this condition (fig. 6*b*). In 40 recent surgical cases we have reviewed, roentgenographic evidence of poststenotic dilatation was lacking in only three patients, and two of these three were less than 15 months old. The poststenotic dilatation usually is localized to the pulmonary trunk, but in some instances the left main branch of the pulmonary trunk also is dilated, the right main branch appearing normal. Fluoroscopically, the dilated pulmonary artery always shows increased pulsation, and in most instances this increased pulsation is fairly marked. Poststenotic dilatation is the most consistent finding in this anomaly, and in many patients, particularly those with mild pulmonary stenosis, it may be the only abnormality evident on the roentgenogram.

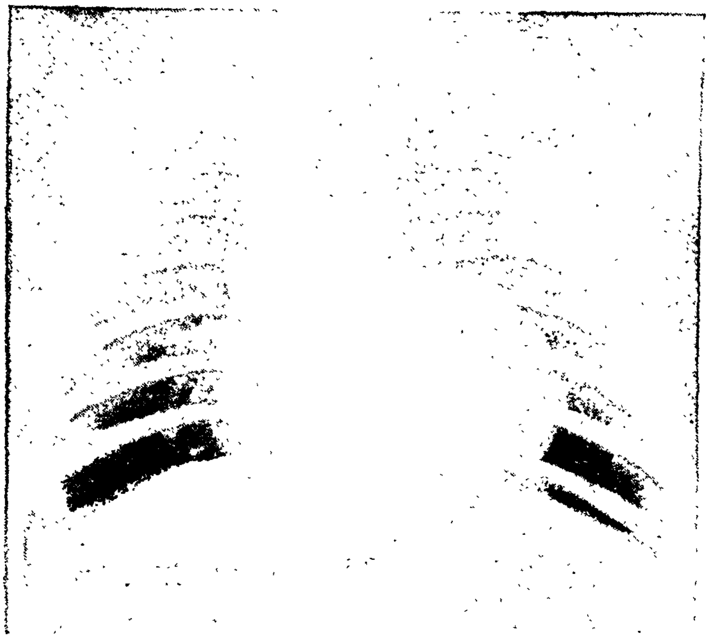

Fig. 7.—Tricuspid atresia: pulmonary vascularity is decreased and pulmonary-artery segment is concave. Note long, flat right-heart border. Cardiac silhouette is strikingly similar to that seen in tetralogy of Fallot, although different ventricles are enlarged in these two conditions.

Although in most instances of pulmonary stenosis with intact ventricular septum the peripheral pulmonary vasculature is normal, in about 20% of patients this vasculature is decreased from normal. Decreased vasculature is usually seen in infants who have severe pulmonary stenosis with an associated interatrial communication and a right-to-left shunt. The presence of poststenotic dilatation of the pulmonary trunk in these patients with decreased vasculature serves to differentiate them from patients with tetralogy, tricuspid atresia, Ebstein's malformation, pseudotruncus, and pulmonary atresia, all of which are characterized by a flat or concave pulmonary-artery segment. Right ventricular enlargement is a fairly consistent finding in functionally significant pulmonary stenosis, as is enlargement of the right atrium.

Tricuspid Atresia.—The roentgenogram of a patient with tricuspid atresia is shown in figure 7. In this condition, there must always be an associated atrial septal defect; blood from the right atrium flows through the defect into the left atrium, then into the left ventricle. From the left ventricle it may reach the lungs by way of a ventricular septal defect and a rudimentary right ventricle and pulmonary artery, or by bronchial arteries arising from the aorta, or by way of a patent ductus. The roentgenographic findings in tricuspid atresia are often quite similar to those in tetralogy of Fallot. Decreased pulmonary vascularity and a concave pulmonary-artery segment are actually more consistently present in tricuspid atresia than in tetralogy. An additional sign sometimes seen on the posteroanterior roentgenogram in tricuspid atresia is a long, flat, right-heart border due to the markedly enlarged right atrium that is usually present in this condition.

Ebstein's Disease.—Ebstein's malformation of the tricuspid valve is another condition to be considered in this group. This anomaly consists of distal displacement of part of the tricuspid valve into the right ventricle. Although the tricuspid-valve ring may be normally situated, the valve leaflets partially arise from the right ventricular wall and ventricular septum and are fused into a membranous structure which extends like a basket down into the cavity of the right ventricle. Part of the right ventricular cavity, therefore, is anatomically and functionally a part of the right atrium, and the functioning right atrium is grossly enlarged. That part of the right ventricle which functions as such is small. Because the tricuspid orifice is usually stenotic and the diastolic capacity of the functioning right ventricle is reduced, pulmonary-blood flow is diminished. A patent foramen ovale is commonly present, and there may be a right-to-left shunt through this defect, with cyanosis.

Although there is nothing pathognomonic about the roentgenographic findings in Ebstein's disease, a large globular heart and clear lung fields are fairly consistent findings in this anomaly (fig. 8*a*).

Pseudotruncus Arteriosus.—Another congenital malformation in which pulmonary vascularity is decreased is so-called pseudotruncus arteriosus. Whereas in truncus arteriosus the pulmonary arteries arise from a single common arterial trunk, in pseudotruncus, sometimes called truncus type II, there is complete absence of the pulmonary arteries, and the pulmonary circulation is by way of bronchial arteries arising from the enlarged thoracic aorta. Whenever a wide and unusually prominent ascending aorta and aortic arch are seen in association with decreased pulmonary vascularity and the central pulmonary arteries cannot be defined, the diagnosis of pseudotruncus should be suggested (fig. 8*b*).

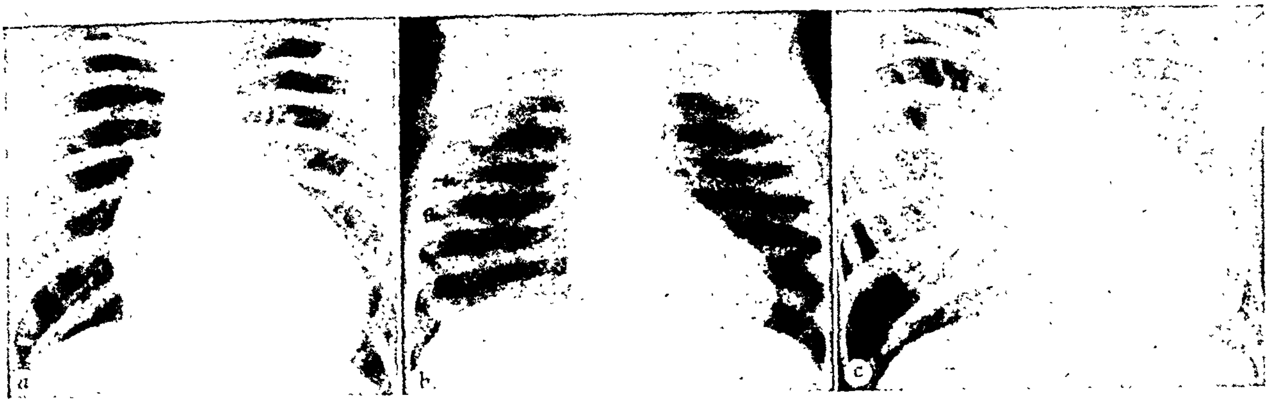

Fig. 8.—*a*, Ebstein's malformation of tricuspid valve: Note large globular heart and diminished pulmonary vascularity. *b*, pseudotruncus arteriosus: Aorta is much larger than normal, and lung fields are clear. There are no pulmonary arteries, and pulmonary circulation is by way of bronchial arteries arising from aorta. Left ventricle is enlarged. c, congenital absence of left main branch of pulmonary artery: There is hypoplasia of left lung. Blood supply to left lung is by way of bronchial arteries. Compensatory enlargement of right pulmonary artery is evident.

Congenital Absence of Branch of Pulmonary Artery.—Congenital absence of either the right or the left main branch of the pulmonary artery is a relatively rare condition which produces unilateral decrease in pulmonary arterial vascularity. Characteristically, as shown in figure 8*c*, the hilar and peripheral branches of the pulmonary artery cannot be visualized on the involved side, and in this instance, although there appear to be many vessels in the left lung, the entire blood supply to this lung is by way of dilated bronchial arteries. There is frequently compensatory hypertrophy of the opposite main branch of the pulmonary artery, and the hemithorax on the involved side is small, with shift of the mediastinal structures to this side. Whenever these findings are encountered, congenital absence of a main branch of the pulmonary artery is likely. This condition is always associated with hypoplasia or agenesis of some of the segments of the involved lung. Angiocardiography and bronchography are necessary for an exact anatomic diagnosis.

Conditions with Normal Pulmonary Vascularity (Normal Flow)

Although a large number of cardiovascular malformations could be included in a complete list of anomalies associated with normal pulmonary vascularity, only a few are of any great functional significance. The only common operable lesions in this group are coarctation of the aorta and congenital aortic stenosis. It is important to recognize, of course, that many of the lesions included in other groups and already discussed are at times associated with normal pulmonary vascularity.

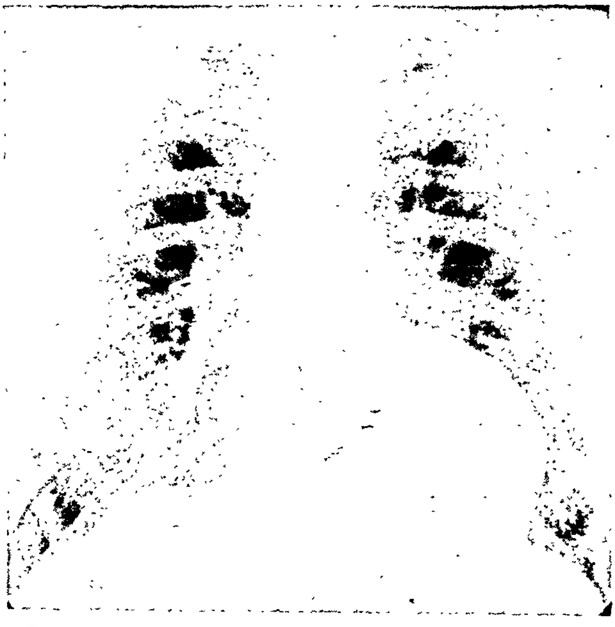

Fig. 9.—Coarctation of aorta showing bilateral rib notching: Site of coarcted segment is visible in descending limb of aortic arch. Left ventricle is enlarged. Pulmonary vascularity is normal.

Coarctation of Aorta.—The diagnosis of coarctation of the aorta may be made from the conventional roentgenogram of the thorax in about 85% of patients with this anomaly. All the characteristic features of coarctation are present in the roentgenogram represented in figure 9; there is bilateral rib notching, and the actual site of the coarcted segment can be seen. Also, the left ventricle is enlarged. In a series of 105 surgically treated patients with coarctation seen at the Mayo Clinic, rib notching was found in 80%, and the site of the coarcted segment could be visualized on the plain roentgenograms in 26%. In infants and children, of course, these characteristic signs are not present, and the diagnosis of coarctation must rest on clinical evidence and demonstration of the lesion by angiocardiography or thoracic aortography.

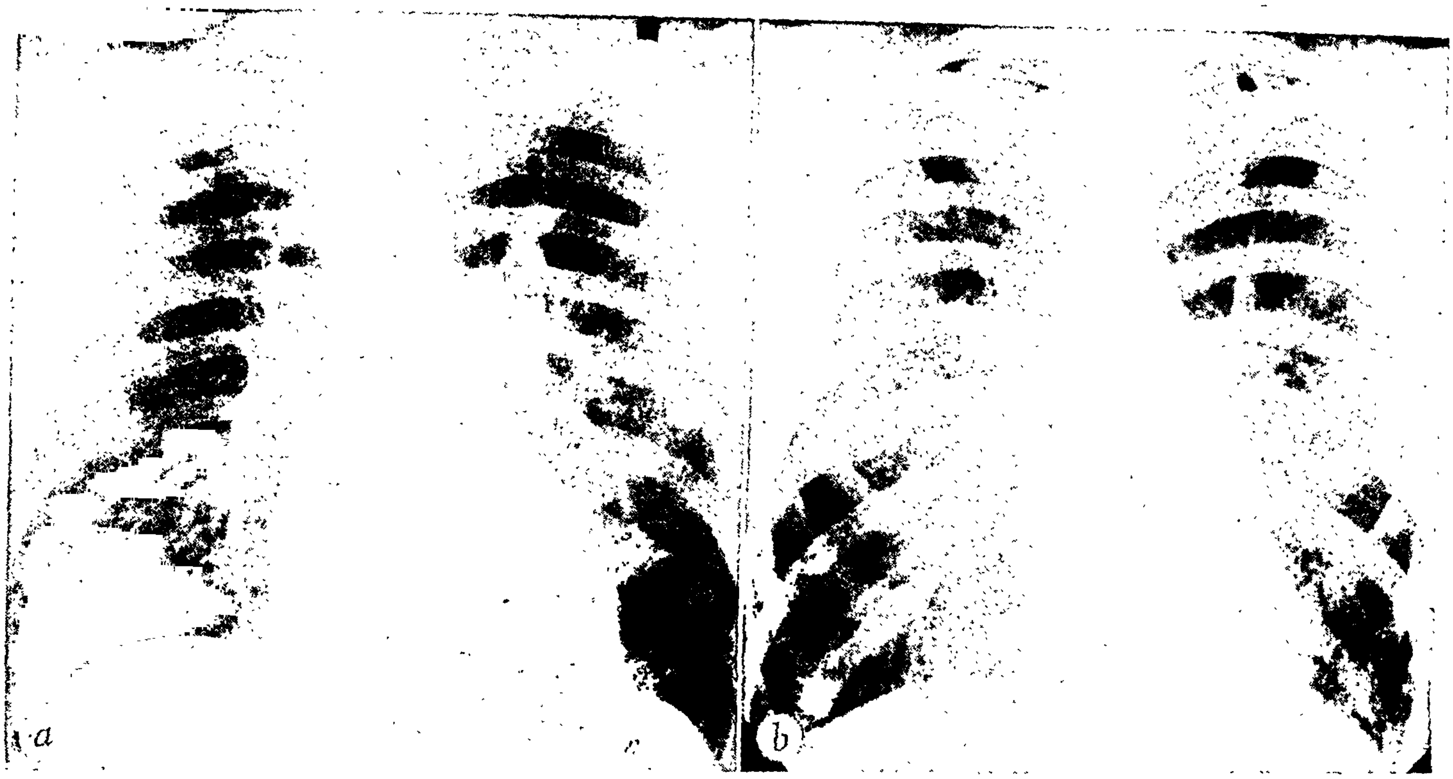

Fig. 10.—*a*, atrial septal defect: There is pulmonary arterial hypertension due to increased pulmonary-artery flow but no pulmonary venous hypertension. Note that outlines of individual vessels are clearly visible. *b*, mitral stenosis: Enlarged hilar vessels and lung fields have hazy, amorphous appearance, and outlines of individual vessels do not show as well. In this condition, there is pulmonary venous hypertension with engorgement of veins and lymphatics, as well as pulmonary arterial hypertension. This arterial hypertension is passive rather than being due to increased pulmonary flow (see text). Hazy appearance of lung fields is best noted in right paracardiac region. This area is comparatively clear in patient with atrial septal defect

Congenital Aortic Stenosis.—The roentgenologic manifestations of congenital aortic stenosis are similar to those of acquired aortic stenosis. Findings consist of a varying degree of left ventricular enlargement and calcification of the aortic valve. While calcification of the valve is rarely, if ever, seen in children, such calcification is not uncommonly encountered in adults with congenital aortic stenosis. Another common finding is prominence of the ascending aorta due to poststenotic dilatation.

Conditions Causing Pulmonary Venous Hypertension (Obstruction to Pulmonary Venous Flow)

Obstruction to venous return from the lungs occurs in left-heart failure from any cause, but the important operable, congenital anomalies that most consistently produce this are congenital mitral stenosis and congenital stenosis of the pulmonary veins, the latter condition being relatively rare.

Congenital Mitral Stenosis.—The roentgenologic findings in congenital mitral stenosis are exactly the same as those in acquired mitral stenosis. In mitral stenosis with marked left atrial enlargement or calcification of the mitral valve and with the classic pulmonary signs of chronic pulmonary venous hypertension, diagnosis is not difficult. However, in early mitral stenosis in which the only abnormal findings are slight left atrial enlargement and engorgement of the hilar vessels, differentiation from a congenital anomaly with pulmonary hypertension, such as septal defect, may seem to offer some difficulty. In mitral stenosis, however, the appearance of the pulmonary vessels is different from that seen in patients with congenital heart disease and pulmonary hypertension due to increased pulmonary artery flow (fig. 10). The roentgenogram shown in figure 10*a* is that of a patient with atrial septal defect; the individual outlines of the engorged pulmonary arteries can be well seen. In this condition, of course, there is only pulmonary arterial hypertension and no pulmonary venous hypertension. The roentgenogram shown in figure 10*b* is that of a patient with mitral stenosis. Here the enlarged hilar shadows and the lung fields have a hazy, amorphous appearance, and the outlines of individual vessels do not show as well. This is due to the fact that in mitral stenosis there is not only pulmonary arterial hypertension but also pulmonary venous hypertension, with engorgement of veins, lymphatics, and arteries. This hazy appearance of the pulmonary vessels is best noted in the right paracardiac region, since this is where the engorged pulmonary veins cross medially just below the pulmonary arteries before entering the left atrium. This area is quite clear in the patient with atrial septal defect, since the veins are not distended.

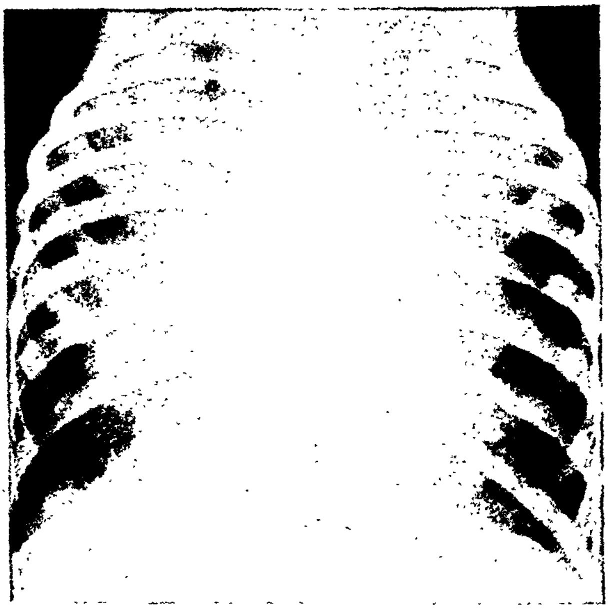

Fig. 11.—Congenital stenosis of pulmonary veins: appearance is that of pulmonary edema.

Another important differentiating feature is the pulsation of the hilar arteries as seen fluoroscopically. Pulmonary arterial hypertension in mitral stenosis occurs as a passive or secondary phenomenon. In other words, when the pulmonary venous pressure increases, the pulmonary arterial pressure rises secondarily to maintain a certain pressure gradient across the pulmonary capillary bed, and not because of increased pulmonary flow. A poorly understood vasconstrictive reflex mechanism, causing constriction of the peripheral pulmonary arteries, also plays a major role in the production of pulmonary arterial hypertension in mitral stenosis. Thus, in mitral stenosis, the pulmonary arteries usually do not show increased pulsations and their pulsations are often diminished from normal. In septal defect with increased pulmonary-artery flow, the pulmonary-artery pulsations are, of course, markedly increased.

Congenital Stenosis of Pulmonary Veins.—Congenital stenosis of the pulmonary veins, at or near their entry into the left atrium, is a rare anomaly that produces severe and rather acute pulmonary venous hypertension, usually evident soon after birth. Although this anomaly is rare, it is important in that its early recognition may be lifesaving. While this condition produces a confusing clinical picture, the roentgenographic findings are frequently characteristic; they are similar to those of acute pulmonary edema. Actually, pulmonary edema is undoubtedly present in these instances as a result of acute severe pulmonary venous hypertension. My colleagues and I have encountered only a few patients with acute pulmonary venous hypertension due to stenosis of the pulmonary veins, but the features shown in figure 11, although perhaps a little more striking than usual, have been characteristic of most of these cases. Certainly, when the findings of acute pulmonary edema are encountered roentgenographically in an infant, and when the presence of left ventricular failure and uremia can be excluded, one can suggest the diagnosis of congenital stenosis of the pulmonary veins with considerable confidence.

Summary

Roentgenologic examination plays an important role in the diagnosis and surgical evaluation of congenital malformations of the heart and great vessels, and an orderly approach to analysis of the roentgenologic findings in this group if diseases is to be stressed. Such an approach, if the method is to achieve its maximal usefulness, must be based on a fundamental understanding of the pathology and altered hemodynamics of congenital heart disease.

A classification of congenital anomalies into four groups, based on changes in the lesser circulation, and further subdivision based on certain other differentiating features, has proved to be of great practical value from the standpoint of the roentgenologist.

Although in most instances the roentgenologic findings alone are not unequivocally diagnostic of a specific cardiac anomaly, by use of this suggested approach and by correlation of the roentgenologic with the clinical findings in a given patient, an accurate diagnosis can often be established. In many instances, of course, specialized procedures, such as cardiac catheterization, angiocardiography, and thoracic aortography must be used if a precise diagnosis is to be reached.

J.A.M.A., June 11, 1960

CALCIFICATION OF THE VAS DEFERENS IN DIABETES

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and
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The main aim in this study was to determine the incidence of radiographically demonstrable calcification of the vas deferens (CVD) in adult diabetics. The second purpose was to relate the CVD to the severity and duration of the diabetes and to associated vascular calcification. Of 100 male diabetics, 11 had CVD. There was no true correlation between the incidence or duration or severity of diabetes and the associated vascular calcification. CVD is not specific for diabetes but is highly suggestive, certainly more so than is vascular calcification. From the material surveyed in this study it appears that most CVD is related to degeneration in the parietal structure rather than to infection in the lumen of the vas. About 70% of men with CVD can be expected to have diabetes.

Calcification of the vas deferens and seminal vesicles, though rare, has long been recognized. Clement[1] first reported a case of calcification of the seminal vesicles at autopsy in 1830. After this, several other cases of calcification of the seminal vesicles were reported from autopsy findings. In 1893 Orth[2] reported calcification of the vas deferens for the first time at autopsy. The first description of calcification of both vas deferens and seminal vesicles in American literature was by George[3] in 1906. Kretschmer,[4] in 1921, first recognized calcification of a seminal vesicle radiographically, whereas Bianchini[5] was the first to recognize calcification of the vas deferens radiographically, in 1930.

In 1942 Marks and Ham[6] reviewed the world literature on calcifications of seminal vesicles and vas deferens, which included 29 cases; they added 9 new cases. For the first time attention was called to the relationship of diabetes mellitus and calcification of the vas deferens. Seven of their nine cases occurred in diabetic persons. In 1950, Anderson[7] reported calcification of the vas deferens in a male diabetic. In 1951 Wilson and Marks[8] reviewed 60 cases of calcification of the vas deferens and observed that 56 of these were in male diabetics. This group was very select as it was mainly from a diabetes clinic; hence, statistics from this survey would be inconclusive for the over-all male population. Prior to the two papers by Marks, calcification of the vas deferens was thought to be purely due to nonspecific inflammation, tubercular or gonorrheal processes, or degenerative aging. These papers have served to show the close relationship of calcification of the vas deferens to diabetes mellitus, which is now generally accepted.

The vasa deferentia are tubular structures about 12 in. long which start in the scrotum and are continuations of the epididymis. Intrapelvically, they lie medial to the seminal vesicles and between the fundus of the bladder and the rectum (fig. 1). They enter the seminal vesicles medially at the base of the prostate. The vasa store spermatozoa, and the seminal vesicles merely secrete a fluid which suspends the spermatozoa. The female ovarian artery parallels the course of the vas in the male, and in both the pudendal branch of the hypogastric artery is close to the course of the vas but shorter and much smaller in caliber.

Calcifications of the vas deferens, as viewed radiographically, conform to the anatomic topography as expected. These calcifications are parallel lines of densities. Arching over the ureters accentuates these shadows. There have been some cases reported in which even the extrapelvic portions of the vas deferens down to the testicle have been affected.

Report of Investigation

Aims.—The study consisted of the detection of radiographically demonstrable calcifications in the vas deferens and possibly in the seminal vesicles of a group of 100 diabetics picked at random. The calcifications, when found, were classified into three groups: group 1, faint or spotty calcifications of one or both vas deferens on one or both walls; group 2, irregular and moderate calcifications of the vas deferens including both walls; and group 3, dense calcification of vas deferens along entire pelvic portions bilaterally.

Many of the patients were found to have calcifications of the arterial structures of the pelvis and upper part of the thighs. These vascular calcifications were also classified into three groups: group 1, minimal streaky appearance of one or a few pelvic vessels; group 2, moderate calcification of pelvic vessels, some branched ones and some extending slightly into the thighs; and group 3, heavy calcification of the pelvic vessels extending into the thighs.

From the University of Buffalo School of Medicine and the Buffalo General Hospital.

An attempt was then made to relate the severity of diabetes and its duration both with the degree of calcification of the vas deferens and with vascular calcification in the same patients and to note any correlation between calcification of the arteries and that in the vas deferens.

Methods and Materials.—One hundred male patients with known cases of diabetes mellitus were picked at random from the out-patient clinic of the Buffalo General Hospital. Anteroposterior radiographs were made of the pelvic structures when the patients were placed in the supine position. The ages of the patients and the severity and the duration of the diabetes were noted. Classification was made as to degrees of vas deferens and vascular calcifications.

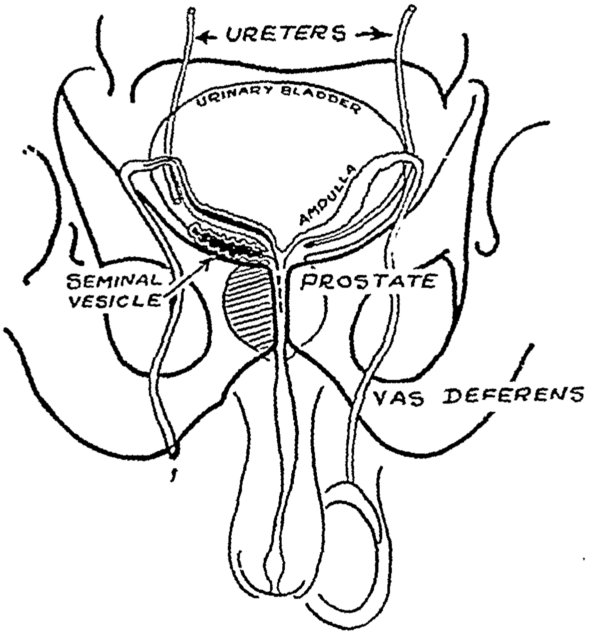

Fig. 1.—Topographic anatomy of vas deferens and seminal vesicle.

Results.—Of the 100 patients studied, 11 had calcification of the vas deferens (table 1). The greatest number, five, was found in the fifth decade. The remaining six were evenly distributed between the fourth and sixth decades. Six patients who had positive cases had associated arterial calcification. The known duration of diabetes was from six months to 33 years.

Of the remaining 89 patients (table 2), the ages varied from 16 to 90 years; the median range was in the fifth decade. Forty-seven, or 53%, did not have radiographically visible vascular calcification. The percentage of patients who had vascular calcification in each decade increased proportionately with increasing years. This was not true of patients who had calcifications of the vas deferens.

Comment

Calcification of the vas deferens is seen in about 11% of adult male diabetics. As can be seen in table 3, there is no correlation between the duration or severity of diabetes and the degree of vas deferens calcification, nor does there appear to be any correlation between the degree of calcification of the vas deferens and calcification of the pelvic arteries.

Table 1.—*Calcification of Vas Deferens in Eleven Diabetic Patients*

	Decade									
Group*	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	Total
1	0	0	0	2	3	0	0	0	0	5
2	0	0	0	1	1	0	0	0	0	2
3	0	0	0	0	1	3	0	0	0	4
Total	0	0	0	3	5	3	0	0	0	11

* See text for explanation of groups.

Table 2.—*Vascular Calcification and No Vas Deferens Calcification in Eighty-nine Diabetic Patients*

	Decade									
Group*	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	Total
†	0	1	8	9	11	10	6	1	1	47
1	0	0	1	1	6	9	4	0	2	23
2	0	0	0	1	3	1	2	2	0	9
3	0	0	0	0	2	1	6	1	0	10
Total	0	1	9	11	22	21	18	4	3	89

* See text for explanation of groups.
† No calcification.

Table 3.—*Data on Patients with Calcification of Vas Deferens*

		Diabetes			Severity of Calcification, by Groups	
		Duration,	Dosage, Units			
Case	Age, Yr.	Yr.	NPH*	PZI†	Vas Deferens	Vascular
1	54	4	15	..	3	1
2	62	33	100	..	3	1
3	53	14	30	..	2	None
4	58	17	‡	‡	1	3
5	63	19	..	20	3	2
6	41	4	..	80	1	1
7	60	§	‡	‡	3	None
8	50	½	70	..	1	None
9	49	25	..	30	2	None
10	47	15	64	..	1	1
11	51	1½	Tolbutamide		1	None

* Modified protamine insulin.
† Protamine zinc insulin.
‡ Controlled by diet.
§ Unknown.

Table 4.—*Data on Incidental Nonselected Series of Patients*

				Severity of Calcification, by Group	
Case	Age, Yr.	Duration of Diabetes, Yr.	Therapy	Vas Deferens	Vascular
12	66	None	..	3	None
13	69	7	Tolbutamide, t.i.d.	1	1
14	52	7	Diet	1	1
15	46	None	..	1	None
16	60	2	Diet	2	1
17	51	None	..	2	None
18	51	None	..	2	None

While this study was in progress, seven other patients with calcifications of the vas deferens were seen in a nonselected group who had routine roentgenograms taken, that showed pelvic structures (table 4). Three had diabetes, three were nondiabetic, and one (case 15) gave a history of syphilis and other venereal disease but no diabetes. The type of calcification in this patient was quite different from that seen in all other cases reported in this study. The usual calcification of the vas deferens in this group was a typical wall type of calcification (the superior wall is the one which most frequently has minimal calcification). Most patients have calcification from the point where the vas deferens crosses the ureter to its junction with the seminal vesicle. At the most lateral portion of the calcification, the appearance is that of a ring due to the doubling over the tube at its crossing of the ureter (fig. 2). It would seem from the appearance of the calcification and from previously reported histology that this is a typical dystrophic calcification of degeneration as seen in arterial structures.

This is true in degenerative disease of the vas deferens, whether in a diabetic or nondiabetic. The same rule seems to apply to the vas deferens as to arteries; the process is more advanced and severe in diabetics. The dystrophic calcification is not a part of diabetes but a part of the general degeneration of the disease. However, dystrophic calcification of the vas deferens is more specific than calcification of the arteries in the diabetic. From literature and our observation it would seem that calcification of the vas deferens is diagnostic of diabetes in about 70% of males who have it.

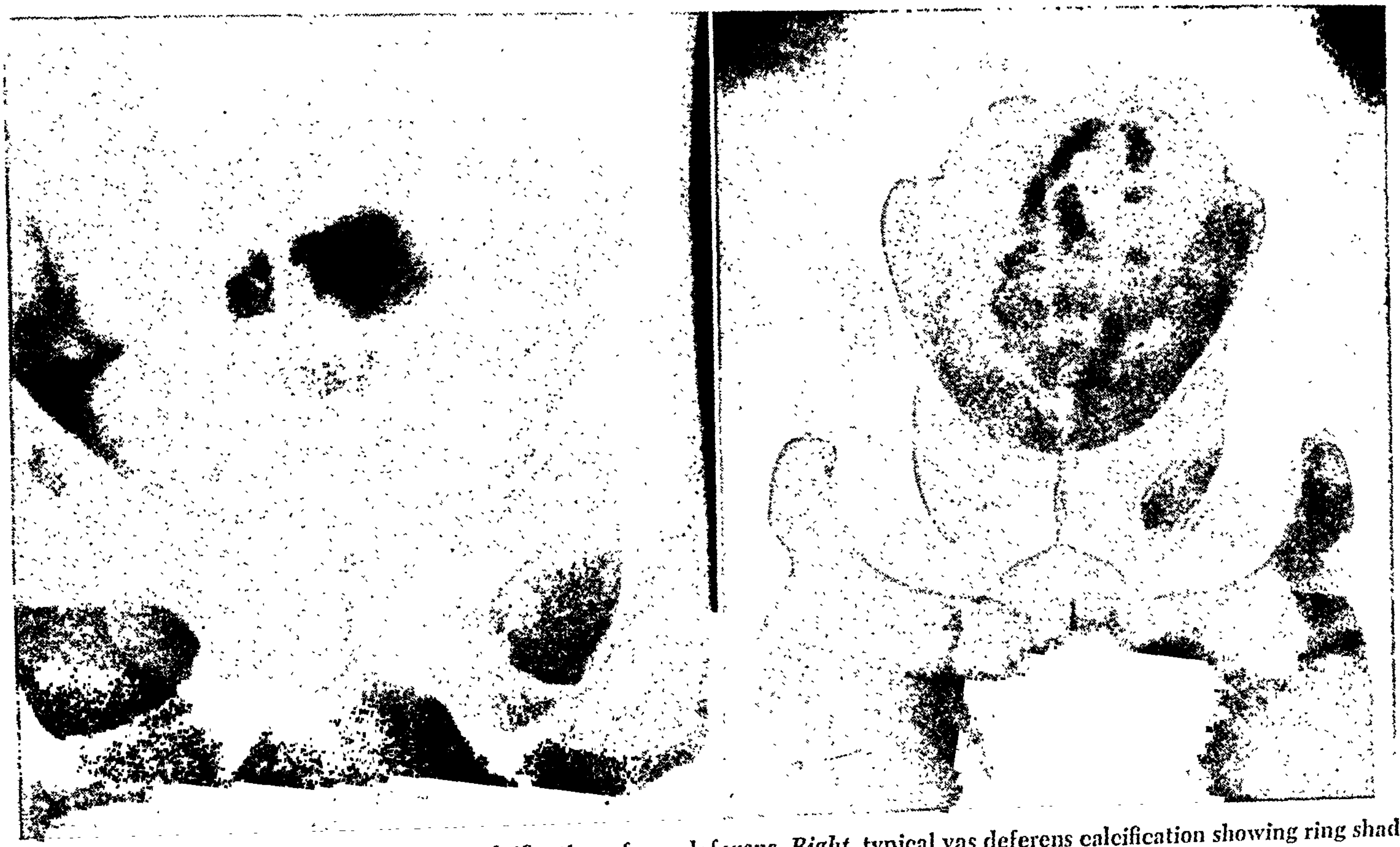

Fig. 2.—*Left*, typical plaque-like wall calcification of vas deferens. *Right*, typical vas deferens calcification showing ring shadows at the point of crossing the ureters.

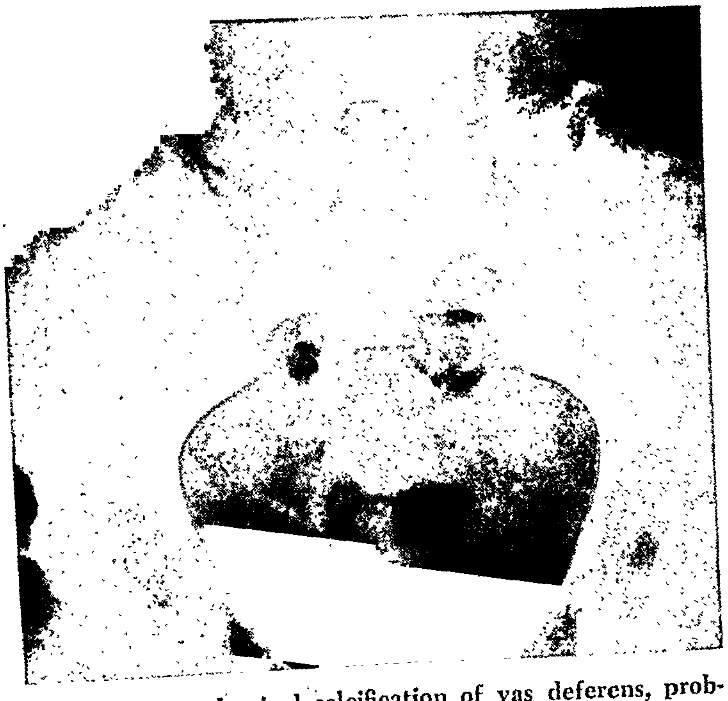

Fig. 3.—Intraluminal calcification of vas deferens, probably postinfectious.

It is necessary to comment on the probable difference between degenerative calcification of the vas deferens and that resulting from infection. The calcification from infection is more intraluminally occlusive and does not occur in the wall (see fig. 3). The over-all different appearance is obvious.

Conclusions

Slightly over 10% of adult male diabetics will show radiographically demonstrable calcification of the vas deferens. Calcification of the vas deferens is not specific for diabetes, but it is highly suggestive. There is no correlation between duration or severity of diabetes and the presence of calcification of the vas deferens. There is no correlation between calcification of the vas deferens and of the arteries. The roentgenographic appearance of degenerative calcification of the vas deferens and that associated with infection is quite different.

100 High St. (3) (Dr. Culver).

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THERMAL DECOMPOSITION OF ETHER IN THE INFANT INCUBATOR

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The observation that infants placed in an incubator after surgery sneezed and coughed, and that a pungent odor was generated within the incubator, led to a search for possible irritants. It was found that diethyl ether, exhaled by the infant during recovery from anesthesia, could be decomposed by contact with the electrical heating element in the incubator. In experiments with rabbits recovering from ether anesthesia and placed in the incubator, formaldehyde was found to be produced in concentrations as high as 370 ppm, far exceeding the threshold limits set for industrial atmospheres. The production of such irritants can be avoided with use of a heater so designed that the gases in the incubator do not come into contact with heating elements at high temperatures.

Several types of incubators are available to provide warmth, moisture, and an oxygen-enriched atmosphere for infants in the postoperative period. When ether has been used as the primary anesthetic agent, however, a potentially serious problem may arise from decomposition of exhaled ether vapor by the heating element of the incubator.

Brooke Army Hospital has several incubator units available for use in the postanesthetic recovery suite. Until recently these units were used during the immediate postoperative period to provide infants with the environmental advantages mentioned above. It was noticed by anesthesia and recovery suite personnel that when an infant who had received ether as the primary anesthetic agent was placed in the incubator unit, a pungent odor, unlike that of ether alone, was generated. Occasionally, coughing, sneezing, and other signs of respiratory tract irritation were manifested by the patient while in the incubator atmosphere. The identity of the substance was suspected and then it was determined by qualitative methods that formaldehyde gas was present in detectable quantities under these conditions. Further studies were made to determine the significance of this occurrence and its possible effect on the patient.

The incubator tested is equipped with a hinged rectangular plastic hood with arm-hole diaphragms in the front and rear through which the infant can be handled. A water humidification reservoir, a circulating fan, and a heating unit are located beneath the mattress for control of the internal environment. The heating unit utilizes a high-temperature element and is thermostatically controlled.

Method

The exact process by which ether decomposes to aldehydes is complex and somewhat obscure. At high temperatures formaldehyde is the major product of diethyl ether decomposition.

Lundgren[1] has extensively studied the autooxidation of diethyl ether within normal temperature ranges. The most prevalent products of decomposition he found were ether peroxides, acetaldehyde, and acetic acid. Lemay and Ouellet[2] studied the oxidation products at temperatures up to 175 C by passage of ether vapor over a nickel catalyst. They suggested several possible routes by which the products listed above may be formed; however,

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these are too lengthy to reproduce here. Formaldehyde was not specifically listed as an end-product by any of these authors.

It is possible that acetaldehyde is the precursor of formaldehyde. According to a scheme worked out by Grumer,[3] acetaldehyde undergoes pyrolysis at high temperatures in the presence of oxygen to form methanol, water, and carbon dioxide. Methanol is easily decomposed over a hot catalytic surface in the presence of oxygen to form formaldehyde gas in the incubator.

TABLE 1.—*Results of First Experiment to Determine Formaldehyde Concentration in Incubators*

Sampling Time, Min.	Incubator Temperature, F: Initial	Incubator Temperature, F: Final	Heater	Formaldehyde Concentration: Mg./Cu. Ft.	Formaldehyde Concentration: Ppm
0-10	76.2	79	On	0.40	11
14-24	79.0	81	On	1.90	55
25-35	81.0	81	On	6.69	192
36-46	81.0	81	Off	2.29	66
47-57	81.0	81	Off	2.91	84

In this study, formaldehyde concentration was determined by the Goldman-Yagoda method.[4] Formaldehyde gas from the incubator was collected with use of a midget impinger at a sampling rate of 0.1 cu. ft. per minute. Samples were taken over serial 10-minute periods in order that 1 cu. ft. of the incubator atmosphere could be analyzed. About 10 cc. of a neutral solution of 1% sodium bisulfite was placed in the impinger and air was drawn through it with use of a vacuum pump attached to a pressure gauge calibrated with a wet test meter, and the pressure was adjusted to provide a flow of 0.010 cu. ft. per minute.

In the first experiment, liquid anesthetic ether was placed in an evaporating dish in which a wisp of cotton was also placed to increase the evaporation rate of the ether. The dish was then placed within the incubator and the unit was turned on to the automatic temperature control position to give about 80 F. Samples of the atmosphere from within were collected for 10-minute periods over an interval of about 57 minutes. The incubator temperature increased from 72.5 to 81.0 F during this time, and temperature of the heating element increased from room temperature to about 480 C (896 F), then gradually cooled to chamber temperature. The results of these experiments are shown in table 1.

TABLE 2.—*Results of Experiment on Temperature Required for Thermal Decomposition of Ether*

Temperature of Heater Element: C	Temperature of Heater Element: F	Formaldehyde Concentration: Mg./Cu. Ft.	Formaldehyde Concentration: Ppm
120	248	...	...
150-160	302-320	0.42	12
280-335	536-635	3.24	91

A second experiment was designed to determine the minimum quantity of ether which must be vaporized in the incubator with the heater on to give the characteristic odor of formaldehyde. After 0.26 Gm. (0.36 cc.) of ether was vaporized within the incubator, which has a volume of about 5 cu. ft., the formaldehyde odor was detectable, and the incubator atmosphere gave a positive result of the fuchsin-bisulfite spot test[5] for formaldehyde at this point.

The next experiment carried out was planned to determine the temperature required for the thermal decomposition of ether into formaldehyde. This was done by sealing the incubator heater element in an airtight glass unit over which air saturated with ether vapor could be passed. The formaldehyde produced was measured quantitatively by the method described previously.[4] The results of this study are shown in table 2.

From the experiment described, little doubt is left that the source of formaldehyde production in the unit is thermal decomposition of ether by contact with the heating element. Catalytic factors from materials used in the construction of the heating element may also contribute to the chemical reaction. This aspect of the problem was not investigated.

TABLE 3.—*Results of Experiment to Determine Effects of Formaldehyde Concentrations on Rabbits*

Rabbit, No.	Weight, Lb.	Duration of Anesthesia, Min.	Incubator Temperature, F: Initial	Incubator Temperature, F: Final	Heater	Formaldehyde Concentration: Mg./Cu. Ft.	Formaldehyde Concentration: Ppm
1	6.50	40	78	81	On constantly		
Control						0.09	2.5
1st 10 min.						1.67	47.0
2nd 10 min.						3.76	106.0
3rd 10 min.						3.42	98.0
50-60 min.						0.39	11.0
2	5 75	30	79	82	On for 1st 5 min.		
Control						0.06	1.7
1st 10 min.						0.97	27.0
2nd 10 min.						0.84	24.0
3rd 10 min.						0.27	7.6
50-60 min.						0.12	3.4
3*	6.50	45	76	82	On for 1st 50 min.		
Control						0.10	2.8
1st 10 min.						9.00	254.0
2nd 10 min.						4.80	136.0
3rd 10 min.						3.50	98.0
50-60 min.						13.10	370.0

* This rabbit manifested respiratory depression and excess secretions in early recovery period. No atropine was given as preanesthetic medication.

Other experiments, which will not be tabulated, in which in vitro ether vaporization was used, confirmed that formaldehyde concentrations as high as 13.94 mg. per cubic foot or 394 parts per million (ppm) could be reached within the incubator atmosphere, depending on the relative time of activity of the heating element during the sampling period.

In the final phase of the study, each of three adult rabbits was anesthetized to surgical planes with open drop ether and then placed in the incubator, with a flow of 6 liters of oxygen and full humidity. Samples of the atmosphere within the incubator were taken for three 10-minute periods and for one final 10-minute period during the first hour. The conditions of each part of the experiment and the results are shown in table 3. Each rabbit was removed from the incubator at the end of the sampling period.

Rabbit 3 was killed 48 hours after the experiment and its lungs were prepared and sectioned for microscopic examination. Only minimal inflammatory reaction in the form of interstitial white blood cell infiltration was noted. It should be emphasized, however, that exposure to the formaldehyde was limited to one hour.

Comment

It is well known that high temperatures cause ether to decompose. The decomposition products include formaldehyde, acetaldehyde, methanol, and peroxides of ether. All of these products are potentially toxic. At high temperatures, formaldehyde is one of the major end-products of decomposition.

Formaldehyde is recognized as a health hazard in industrial plants. The gas is a powerful irritant to the respiratory tract and may give rise to chemical pneumonitis. Chemical pneumonitis is characterized[6] by inflammation of the bronchi and alveoli, with edema, immigration of cells, and deposits of fibrin within 4 to 24 hours after exposure. The bronchial and alveolar epithelium may be desquamated. A hyaline membrane may be formed on the alveolar wall from coagulation of fluid. Secondary bacterial infection may appear after several days.

In the United States and England the maximum allowable atmospheric concentration is generally set at 0.012 mg. per liter or 10 ppm. The threshold adopted by the American Conference of Governmental Industrial Hygienists[7] is 5 ppm. In all experiments described, this allowable maximum was exceeded.

In the experiments with rabbits under normal operating conditions of the incubator, formaldehyde concentrations as high as 370 ppm were reached in the incubator atmosphere. It is reasonably certain that equally high concentrations of formaldehyde may be reached in the incubator when an infant of comparable size and weight who has received an ether anesthetic is placed in the unit.

An incubator of different manufacture in which a completely shielded heating element is used was tested qualitatively at a later date. This was found to be free of products of ether decomposition under ordinary operating conditions. The critical temperature for decomposition of ether was not reached by the exposed portion of the heating mechanism. It is possible that there are many incubator units, in which high-temperature heating elements are used, which would lead to ether decomposition. Additional models were not available for investigation in this study.

Recommendations.—We believe the incubator tested to be a valuable instrument for the care of infants. The unit is still used for postoperative care when agents other than ether have been used for anesthesia. Possible ways to circumvent the difficulties we have encountered after ether anesthesia and placement of the patients in the incubator have been considered. First, if a lower temperature heating unit could be used for the immediate postoperative period, the amount of exhaled ether vapor would decrease to lower and safe limits, at which time the infant could be placed in the incubator. Second, since the activity of the heating element appears to be the main factor leading to the decomposition of the ether, the incubator should be allowed maximum time to reach an equilibrium temperature or should be placed in a warmer portion of the recovery suite so as to reduce to a minimum the activity time of the heating element. The effect of higher oxygen flows used to "dilute" the formaldehyde has not been worked out. It is probable that this may cause additional cooling of the incubator atmosphere and likewise additional activity time of the heating mechanism to decompose additional ether.

Summary

The potential hazard of formaldehyde production through thermal decomposition of ether in an infant incubator has been studied. Adult rabbits anesthetized with open drop ether were placed in the incubator under ordinary operating conditions of the unit. Formaldehyde concentrations as high as 370 ppm were reached. Limits of concentration for formaldehyde gas in industrial plants are set within the range of 5 to 10 ppm. Toxic effects on the respiratory tracts of postanesthetic patients may result from the formaldehyde concentrations reached in the incubator.

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CYSTIC ADVENTITIAL DEGENERATION OF THE POPLITEAL ARTERY

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A rare arterial occlusive disease, characterized by cystic changes in the wall of the popliteal artery, was first described by Erjup and Hiertonn in 1954.[1]

Clinical Pathological Picture

The clinical pathological picture of the disease has been remarkably uniform. All cases of cystic degeneration of the popliteal artery have occurred in young men between 24 and 47 years of age. In each case, there was sudden onset of pain in the calf without history of trauma or other apparent cause. This pain was followed by claudication of the involved leg. There has been in each patient an absence of the usual evidence of general arterial obliterative disease. There has been arteriographic evidence of stenosis or occlusion of the popliteal artery. Operative findings have revealed an intramural cyst compressing the arterial lumen. The gross findings have been similar in each patient, with a cystlike formation in the wall of the artery. The cyst has the general appearance of a ganglion and contains jelly-like material which is under pressure. This peculiar abnormality, which is not described in the common textbooks of pathology or surgery, represents a newly recognized clinical entity or disease which involves occlusive compression of the popliteal artery by an intramural cyst originating in the adventitia of the artery. There is no gross sign of the usual atheromatous changes. Microscopic examination, as reported by Hiertonn and Lindberg,[2] showed no evidence of atheromatous changes. The cysts were located in the adventitia of the popliteal artery. Chromatographic analysis of the mucinous substance in the cyst revealed mainly hyaluronic acid components and occasionally amino acids but no carbohydrates, cholesterin, or calcium.

The specimen in this case was a cystic mass, lobulated and ovoid, measuring 4 by 2 by 1 cm., and filled with a mucinous cloudy material. The wall was thin and the lining smooth. Microscopically, the cyst was lined by degenerated fibrous tissue covered by fibrin and fibrinoid material.

Report of a Case

A 42-year-old mechanic was first seen in November, 1957. About six weeks prior to this time, the patient had noted sudden onset of pain in his left calf followed by numbness of the foot and toes. These symptoms occurred after repeated kneeling during his work. The original pain, paleness, coldness, and numbness subsided after several hours, but there was some residual tenderness of the calf muscles for one week. The patient stated that from that time on, he had cramps in his left calf on walking one flat block.

Physical examination showed that he was a graying, young-appearing, and exceptionally muscular young man who was in no apparent distress. The general physical examination was noncontributory and gave quite normal findings. The blood pressure was 130/72 mm. Hg. Early arcus senilis was noted. Examination of the right lower extremity revealed normal femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Examination of the left lower extremity revealed a normal femoral pulse which was equal to the right, but all pulses below the femoral pulse were absent. The left foot was white and cold. When elevated, it became cadaveric, and when it was resting color returned abnormally slowly.

The patient was admitted to the hospital, and a femoral percutaneous arteriogram of the left side, for which 15 cc. of 50% diatrizoate (Hypaque) sodium solution was used, revealed a marked narrowing of the popliteal artery over a distance of 3 to 4 cm. (fig. 1, *left*). It was noteworthy that the narrowing was unusually smooth and uniform as it narrowed the lumen to 2 mm. The vessel above and below the narrow area was quite normal in appearance, without irregularity or other evidence of plaque formation.

On Dec. 5 exploration of the left popliteal artery was carried out. With the patient in the prone position on the operating table, a 7-in. longitudinal incision was made in the midline of the popliteal space. The deep fascia was incised the length of the skin incision, and the popliteal artery was identified. Care was taken not to interrupt the collateral circulation, as the popliteal artery was isolated. In the upper portion of the wound the artery was found to be normal in appearance and pulsation. At the level of the knee joint pulsation ceased, and no pulsation could be felt at any point distal to this.

In this area a firm fusiform mass could be felt which was about 3.0 cm. in length and 1.5 cm. in diameter (fig. 2). This was carefully exposed and

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had the appearance of a clear cyst in the side of the artery. Dissection was carried from the lower end of the cyst proximally, and the cystic structure was excised with the outer layer of the arterial wall itself. As the last band of scar tissue between the cyst and the artery was freed, the full length of the popliteal artery and its branches distal to this area immediately began to visibly pulsate, and some branches that had been transected began to bleed.

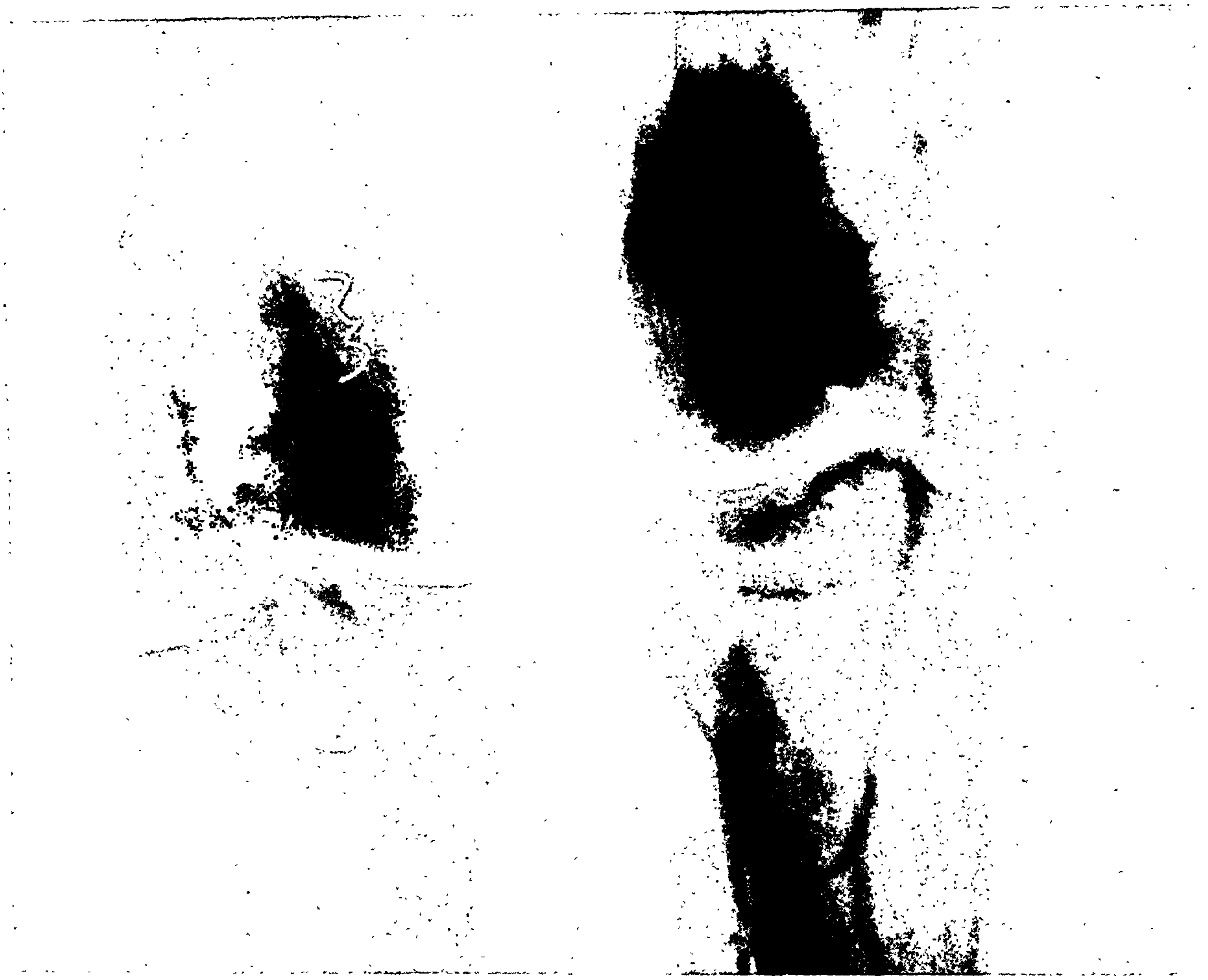

Fig. 1.—*Left*, narrowing of popliteal artery over distance of 3 to 4 cm., shown by arteriogram. Absence of irregularity of artery wall is noteworthy (anteroposterior view). *Right*, after cyst was dissected off artery, arteriogram showed normal flow (posteroanterior view).

It was apparent that the lesion in this case was a rare type of cyst causing occlusion of the popliteal artery lumen by external pressure. An arteriogram taken at this time showed normal findings; the previously described defect was no longer present (fig. 1, *right*). The specimen removed grossly resembled a ganglion (fig. 3). The postoperative course was uneventful, and postoperatively the patient had a strong popliteal dorsalis pedis and posterior tibial pulse on the left. He was completely free of his symptoms and when last seen, 16 months after his operation, had normal pulses on the left side.

Pathogenesis, Cause, and Treatment

In the four patients described by Hiertonn, Lindberg, and Rob,[3] the disease was demonstrated in four stages of development. In one patient the pathology was limited to the adventitia. In this patient the contents of the cyst were described as "like raspberry jelly," and chemical analysis of the jelly showed abundant fibrinogen and carbohydrate-rich globulin and hemoglobin but no increase in calcium and cholesterol. The second patient showed the usual cyst in the adventitia, but the media was partially necrotic. In the third patient the process was still further developed, with rupture of necrotic media and intima. There was a double lumen in the vessel distal to this area. In the fourth the cyst was limited to the adventitia and contained clear jelly-like substance. In a fifth patient, recently reported by Tytgat,[4] the cyst was located in the adventitia and there was marked thinning of the media.

In all patients the cyst containing the jelly-like material was located in the adventitia and changes in the media and intima were apparently secondary, probably due to pressure necrosis. The lumen in each patient was compressed by pressure.

Possible causal factors include hemorrhage, inflammation, or trauma. On the basis of microscopic evidence of the cysts, the first two causes seem unlikely. Trauma in the popliteal area has been recognized by Boyd and others,[5] who suggested that even normal knee movement causes a certain amount of injury. The great amount of motion which occurs in the popliteal artery during flexion and extension of the knee joint has been demonstrated by Lindbom[6] by means of arteriographic examinations. Pathological changes due to repeated microtrauma, secondary to systolic expansion of the vessel wall, were suggested by Palma[7] in 1952 in his study of stenosis and stenotic arteriopathy of Hunter's canal. Similar factors may come into play when the popliteal artery is pinched in an acute angle during extreme flexion of the knee joint.

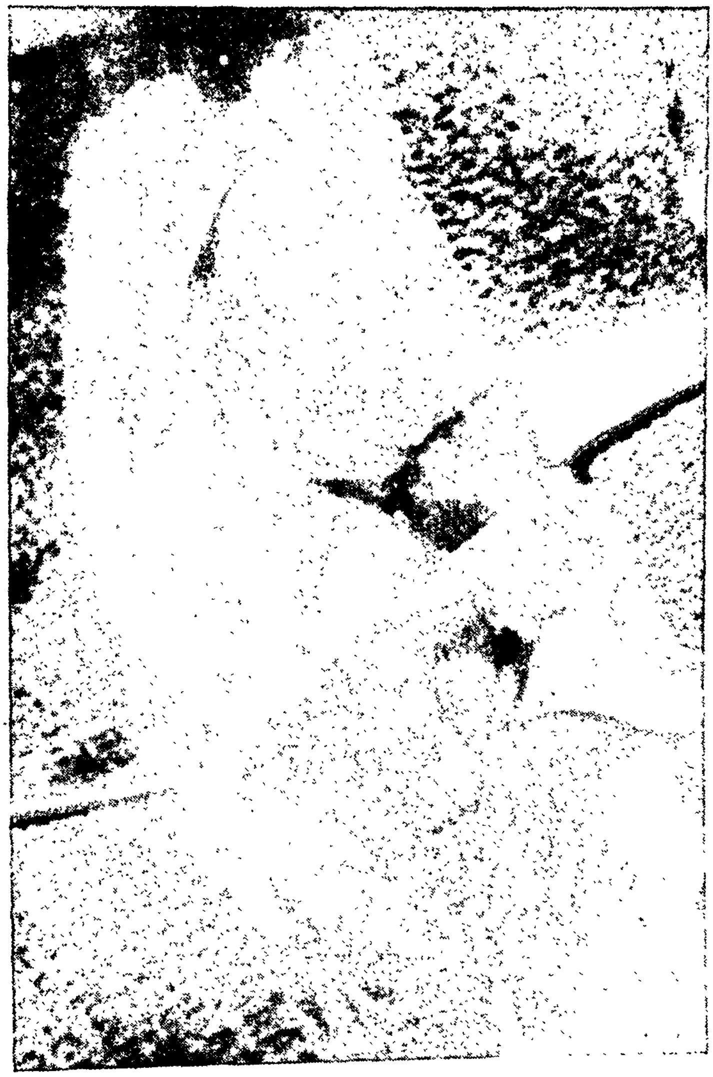

Fig. 2.—Fusiform dilatation of artery in area of cyst.

Cystic lesions in the media of arteries have been noted by Erdheim,[8] but cystic adventitial degeneration as described in this paper differs in many ways from Erdheim's medial cystic necrosis.

In the patient whose case has been reported, the disease was localized to the adventitia. A satisfactory result was obtained by excision of the involved area of the adventitia, leaving the artery intact. Of the four patients described by Hiertonn, three were treated by autogenous vein graft and one was treated by homologous artery graft. The patient reported by Tytgat was treated by nylon graft. All patients had complete restoration of circulation.

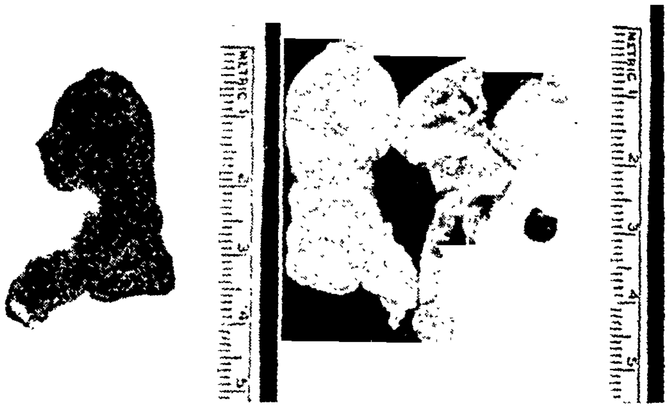

Fig. 3.—*Left,* intact specimen, which grossly resembles ganglion, and, *right,* sectioned specimen showing gelatinous contents.

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PERSISTENCE OF THE "HYDRALAZINE SYNDROME"

A FOLLOW-UP STUDY OF ELEVEN CASES

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The prolonged administration of hydralazine hydrochloride, an antipressor drug, has been found capable of inducing a syndrome that resembles rheumatoid arthritis or systemic lupus erythematosus. In the past it was assumed that, when administration of the drug was discontinued, the "hydralazine syndrome" would disappear permanently. The follow-up study of 11 cases here reported showed that some of the symptoms and findings persisted for years after administration of the drug had been stopped. In four patients the increased erythrocyte sedimentation rate persisted longer than three years; in two it was associated with continued rheumatic pain, and in the other two it was associated with an unchanging hepatosplenomegaly.

The appearance of a syndrome that simulates rheumatoid arthritis or systemic lupus erythematosus (S. L. E.) after treatment with hydralazine was first described independently by two separate groups of investigators.[1] Since then, 85 cases with "hydralazine syndrome" have been reported. The hydralazine syndrome has been found to occur in 7 to 13% of patients treated with this drug.

Lansbury and Rogers have summarized the characteristics of the hydralazine syndrome. The two phases described by them are (1) the "rheumatoid arthritis" phase, which is characterized by chills and migrating arthralgia combined with myalgia and, subsequently, development of frank arthritis, with symmetrical involvement of the proximal interphalangeal joints and (2) if administration of the drug is continued, progression to the "lupus erythematosus" phase, which is manifested by fever; prostration; pleural, pericardial or synovial effusions; erythematous eruptions resembling those seen in systemic lupus erythematosus, cutaneous sensitivity to ultraviolet light; splenomegaly; and lymphadenopathy.

It has been reported that, if therapy is stopped, either with or without the addition of corticosteroids, the syndrome disappears but may be reactivated by readministration of hydralazine.[2]

Laboratory studies of patients with the hydralazine syndrome may show increased erythrocyte sedimentation rate, transiently false-positive results of tests for syphilis, anemia, neutropenia, and decreased serum albumin and elevated alpha-globulin and gamma-globulin fractions. Lupus erythematosus (L. E.) cells have been reported in 27% of the 85 cases selected from the literature. In most instances, however, the number of L. E. cells found is much less than that usually held to be necessary for a firm diagnosis of systemic lupus erythematosus.

Other types of reactions to hydralazine have been reported but are rare. In one instance, polyarteritis nodosa developed.[3] Two cases have been reported in which polyneuritis developed after prolonged, intensive treatment with hydralazine.[3A] Pancytopenia has been noted twice.[4] In one instance, after administration of small doses of hydralazine, a fatal hypotensive reaction was described.[5] In general, therefore, hydralazine shows little tendency to produce the ordinary types of drug reactions that are thought to be allergic in origin, yet produces a clinical picture which is similar to spontaneously occurring systemic lupus erythematosus.

Prolonged follow-up observations have not been reported but for one instance.[6] This patient maintained a positive L. E. test result for 14 months after hydralazine therapy was stopped. He felt well while on corticosteroid therapy, but the syndrome flared again each time it was discontinued.

The discovery of the "hydralazine syndrome" led to the hope that its study might provide new information concerning systemic lupus erythematosus. Early reports of short-term observations indicated that the syndrome was self-limited. However, since systemic lupus erythematosus characteristically remits and exacerbates, it was decided that only long-term follow-up of hydralazine syndrome cases would determine whether permanent remission was the rule.

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This study concerns 11 previously unreported patients, whose progress has been followed for an average of six years. Certain unique features of this group will be emphasized, the most important of which seems to be the prolonged persistence, in an active state, of aspects of the syndrome.

Subjects and Procedures

The 11 patients were seen at the time of their first reaction to hydralazine. Subsequently, they were observed for three to seven years, at varying intervals. Careful clinical examinations were carried out frequently. In addition, over the past three years, at least three thorough clinical and laboratory examinations were made on each patient, with special attention to the possible persistence of the hydralazine syndrome. These examinations consisted of taking a detailed history, a physical examination, and the laboratory studies summarized in table 1.

Table 1.—*Laboratory Findings in Eleven Patients with Hydralazine Syndrome*

Study	During Syndrome		After Syndrome	
	No. of Subjects	Positive Findings	No. of Subjects	Positive Findings
Anemia (hemoglobin level less than 13 Gm./100 cc.)	9	5	11	0
Leukopenia (WBC less than 5,000)	9	1	11	0
Thrombocytopenia (less than 150,000/cubic millimeter)	5	1	11	0
Erythrocyte sedimentation rate	7	6	11	7
L. E. preparation	7	2	11	0
Albuminuria	9	0	11	0
Abnormal urine sediment	9	6	11	0
Result of serologic test for syphilis (Kolmer & Kline)	8	5	11	0
Abnormal liver flocculation test results	8	5	11	1
Low serum albumin level	10	4	11	0
Increased serum globulin level	10	4	11	0
Result of Coombs test (direct & indirect)	2	0	11	0
Abnormal coagulogram*	2	0	11	0
Changes in electrocardiogram	11	0	11	0

* Coagulogram consists of: clotting time, bleeding time, clot retraction, and one-stage prothrombin time. Platlets are noted separately. L. E. cells were sufficiently plentiful to be compatible with a diagnosis of systemic lupus erythematosus.

Patients were included in the series if they presented either the "rheumatoid phase" or the "lupus erythematosus phase" during treatment with hydralazine. None had exhibited similar manifestations prior to the start of hydralazine therapy.

Results.—Previous reports in the literature record a preponderance of men with this syndrome. As in the series of Morrow and associates,[1a] however, 9 of our 11 patients were women. This predominance of women could not be attributed to selection or other artificial factors. The patients (two men and nine women) ranged in age from 24 to 68 years (eight over 40 and three under 40 years of age). Five of them were in the 5th decade of life, which may possibly be related to the peak incidence of hypertension.

The average duration of therapy was 23 months, with all but one subject having received hydralazine for more than one year. This patient received 200 mg. of hydralazine daily for eight months with a total dosage of 48 Gm. Two subjects received total dosages of 60 and 85 Gm., respectively, over 18 and 14 months. The remaining subjects all received over 100 Gm., with an average of 273 Gm., of hydralazine prior to the onset of symptoms. The average daily dose of drug being ingested at the onset of symptoms was 450 mg. The signs and symptoms observed are summarized in the following brief description.

Summary of Clinical Picture.—In 8 of 11 patients, the appearance of symptoms was closely related in time to a favorable therapeutic response in blood pressure.

When chest pain was present, it appeared 1 to 12 months before any of the other manifestations of the syndrome. It generally lasted for hours at a time and was unrelated to effort, respiration, or position. It was described as diffuse and oppressive in character. No electrocardiographic changes were associated with this pain. In all subjects, the pain disappeared promptly when medication was discontinued.

Report of Cases

Case 1.—The progression from mild arthralgia to a rheumatoid-like arthritis and then to a febrile, systemic disease was clearly observed in the first patient of this series. The cause of her complaints was not recognized, and she remained on hydralazine therapy until she developed the last and most severe stage of the syndrome. The syndrome presented itself with anorexia, chills, fever to 103 F (39.4 C), sweating, joint pains, and weight loss. This was associated with development of a butterfly facial rash and a positive result of an L. E. test. At this stage, in September, 1952, administration of hydralazine was stopped; cortisone was administered for six weeks, and the patient's condition improved to the level attained at the time of writing. Currently, seven years after the cessation of hydralazine therapy, she notes only occasional, mild aching of her knees. Laboratory evaluation shows a persistently high erythrocyte sedimentation rate. In March, 1957, one L. E. preparation contained three possible L. E. cells, but this finding was not conclusive. Several other L. E. preparations examined as recently as 1959 have been completely negative.

Cases 2-7.—In four patients, all symptoms subsided within 24 to 48 hours after discontinuance of hydralazine therapy. In one patient, the clinical picture persisted for three weeks, and in another subject, for eight weeks after cessation of treatment with hydralazine.

CASE 8.—One patient developed severe, rheumatoid-like arthritis, fever, weakness, chest pain, enlarged spleen, enlarged liver, anemia; results of two L. E. tests were positive. After discontinuation of hydralazine therapy, most of her findings disappeared. When she died three years later at another hospital, however, she was noted to have paralysis agitans, an ataxic gait of unknown etiology, hypertension, diabetes, and persistent hepatosplenomegaly. Autopsy was not performed.

CASES 9-11.—Three subjects, whose progress has been followed for five to seven years, have shown persistent symptoms. Two show active rheumatoid-like arthritis, and one has persistent hepatosplenomegaly.

Three patients were given corticosteroid therapy. In one, treatment was continued for 10 days, in the second for 40 days, and in the third for six months. All these patients have been well since treatment was stopped (table 2).

Laboratory studies at the time of the onset of the hydralazine syndrome were not always as complete as those performed during the follow-up period. In those patients studied during the active phase of the syndrome, the most frequent abnormality was an accelerated erythrocyte sedimentation rate. Albuminuria and changes in urinary sediment were never found (table 1).

Coincidental with the disappearance of symptoms, laboratory values usually reverted to normal. In one patient, who developed the classic syndrome and later appeared to recover completely, a positive thymol flocculation persisted for six years after cessation of hydralazine therapy. The erythrocyte sedimentation rate remained accelerated in two patients who had persistent arthritis, in the two patients with hepatosplenomegaly, and in three others with no sign of disease. It is impossible to determine the significance of the elevated sedimentation rate in the last three subjects. No changes were seen in the blood urea nitrogen levels or in the chest roentgenograms taken during or after the hydralazine reaction.

Comment

The literature is consistent in reporting that the hydralazine syndrome disappears when administration of the drug has been discontinued. Disappearance usually has been reported to occur within days, or at most weeks. To date, however, only one subject's progress has been followed for a prolonged period (14 months).[6] In our long-term study of 11 patients, covering three years in two instances and six to seven years in nine instances, it became evident that aspects of the syndrome can persist for prolonged periods. Therefore, the possibility that a drug can induce systemic lupus erythematosis is raised once again.

Four of our patients seemed to lose all symptoms and signs of the disease, including positive laboratory findings. Two subjects became asymptomatic but continued to run high erythrocyte sedimentation rates. One patient, whose clinical evaluation is negative, maintains positive liver flocculation tests and elevated erythrocyte sedimentation rate. Therefore, in these seven patients, the syndrome was probably self-limited, and, once the signs and symptoms disappeared, they have not shown a tendency to recur.

Most important is the observation that in four patients the active hydralazine syndrome, as measured by both clinical and laboratory findings, has persisted for as long as their progress has been followed since cessation of hydralazine therapy. The duration of the follow-up was three years in two and seven years in the other two instances. The evidence for activity has been active, persistent arthritis of the rheumatoid type, with elevated erythrocyte sedimentation rates in two patients. Two patients have shown unchanging hepatosplenomegaly with elevated erythrocyte sedimentation rates. Laboratory findings, which were originally abnormal, have tended to return to normal with the few exceptions noted, despite other evidence of persistence of the syndrome.

TABLE 2.—*Clinical Findings in Eleven Patients with Hydralazine Syndrome Subsequent to Therapy with Hydralazine*[*]

Symptoms	No. of Patients
Joint pain	11
Joint swelling	5
Chest pain	5
Fever	5
Anorexia	3
Nausea	4
Weight loss	3
Skin rash	3
Hepatosplenomegaly	2
Purpura	1
Duration of symptoms after stopping drug therapy	
1 to 2 days	4
21 days	1
28 days	2
3 to 7 years (at least)	4

[*] Dosage at onset of symptoms, 150 to 800 mg. daily. Duration of therapy, 8 to 36 months.

Thus, it would seem that, regardless of the mechanism involved, some patients with hydralazine syndrome do not remit completely and may show activity or residual manifestations of the syndrome for as long as seven years or more. In our experience, patients who were maintained on hydralazine therapy after development of the full-blown syndrome seemed more likely to show its persistence after cessation of hydralazine therapy. This strongly suggests that it may be of greater importance than has been realized to stop hydralazine therapy at the earliest sign of the syndrome.

The clinical picture of our patients has been similar to that previously reported with the one exception mentioned above, namely, the unusual type of chest pain which, when present, always heralded the onset of the remainder of the hydralazine syndrome by 1 to 12 months. It is important to recognize this fairly common early symptom if one is to stop treatment and presumably arrest the hydralazine syndrome in its earliest phases.

Finally, it seems important to remember that, if any new patients with this syndrome appear, it would be of interest to study them along somewhat different lines with techniques recently made available. For example, the presence of the rheumatoid factor should be evaluated. The studies of Comens,[7] which suggested that trace metal deficiency might play a role in the hydralazine syndrome, should be considered. Renal biopsy might better evaluate renal involvement, since it is recognized that in systemic lupus erythematosus one can find positive histological findings by renal biopsy, despite negative results of urinalyses. Autoimmune antibody-like substances such as those described by Gajdusek[8] should be sought, since high titers are found in systemic lupus erythematosus. In active systemic lupus erythematosus, serum complement tends to decrease and the status of complement in the hydralazine syndrome should be determined. In addition, chiefly through the independent work of Miescher,[9a] Holman and associates,[9b] and Friou,[9c] more detailed methods of studying the lupus factors in serum and white blood cells of patients with systemic lupus erythematosus have been developed. Finally, sytological and chemical studies of joint fluid would be pertinent. Such techniques should be applied to the hydralazine syndrome.

Summary

The progress of 11 patients who developed the hydralazine syndrome has been closely followed for three to seven years. In this group, there was a predominance of women.

Chest pain of a type not previously described in the hydralazine syndrome was noted in 5 of 11 subjects. Early detection of this pain, which usually heralds the onset of the syndrome, suggests discontinuance of use of the drug.

Most important, persistence of some aspects of the hydralazine syndrome was noted in at least 4 of 11 patients several years after cessation of hydralazine therapy. Two patients have suffered from a persistent low-grade rheumatoid arthritis-like condition. Two patients exhibited unchanging hepatosplenomegaly. Laboratory findings, which were originally abnormal, have tended to return to normal with the exceptions noted. As far as one can determine, this presents a unique type of drug reaction, in that hydralazine appears to be a drug able to produce in man a reaction that persists in an active state for years after the medication has been discontinued.

Drs. A. Sellers, J. Hafkenschiel, and A. Lindauer assisted in this study by providing most of the patient material.

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CLINICAL NOTES

CERVICAL COLLAR FOR TREATMENT AND IMMOBILIZATION

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The incidence of painful conditions of the cervical spine is considerable. Various diagnoses are assigned on the basis of the history, physical findings, and roentgenographic findings. These include cervical osteoarthritis, whiplash injury to the cervical spine, fractures of the cervical spine or spinous processes, cervical syndrome, scapulocostal syndrome, discogenic disease or damage, brachialgia stiff-neck syndrome, herniated cervical disk, trapezius myositis, torticollis, and cervical radiculitis. Various types of treatment have been in use for some time. These include medication with aspirin and its derivatives and with the newer muscle relaxant drugs; physical therapy (diathermy, microthermy, galvanism, and other methods); cervical traction; paravertebral blocks; various braces for immobilizing the neck (Thomas Collar, Hittenberger Cervical Brace, Forrester Collar, Lewin Cotton Collar, Victoria Collar); and molded cervical supports of varying types. How helpful these methods are depends on the severity of the condition.

Use of a specially constructed cervical support with a heating pad as the supporting element has been found to be far superior to any method previously available for home use in the treatment of painful conditions of the cervical spine. It consists of a heating pad somewhat like that of a Thomas collar but open in front. It is 18.0 in. long and 3.5 in. wide and has two cloth tapes sewn into its end so that it may be secured around the waist (see figure). The electric cord is long enough (92 in.) to reach an electric outlet or extension cord. The cord has an interrupter switch which has three different heating strengths. The collar is kept in a removable cotton cover which can be laundered.

The patient is instructed to wear the appliance either during sleeping hours or in the evening after supper before retiring or at both these times if his condition is severe. In some situations, it has been used during the day by persons who work at desks. It is far superior to a conventional heating pad because it provides heat and causes immobilization. The conventional heating pads are difficult to use for the cervical spine and almost impossible to use during sleeping hours.

At the time of this writing the collar has been used on over 100 patients with gratifying results. The conditions for which it has been used are listed above. In some patients, it was the only form of treatment; in others, the ones with more severe cases, it was used as an adjunct to office or hospital treatment. The analysis of results would depend on the severity of the situation. In patients with herniated cervical disks it provides palliative relief so that life is tolerable and operation is avoided. In other situations, it produces more rapid cures than were obtainable before its use.

Cervical collar and cover.

99 Lafayette Ave., (17).

From the New York Medical College and the Orthopedic Service of the Coney Island Hospital.

CONGENITAL DISEASE.—The study of human cytogenetics has now attained the stage that the Drosophilists had reached about 40 years ago. We can hardly expect an advance as rapid and dramatic as they achieved in the twenties and thirties, particularly after the rediscovery of the salivary gland chromosomes. Nevertheless there is now a great interest on the part of the medical profession and we can look forward to the screening of large numbers of individuals, at least in Western Europe and North America, and to a steady increase in our understanding of the relationship of chromosomal abnormalities to congenital disease, to neoplasia, and to general human biology.—C. E. Ford, Human Cytogenetics: Its Present Place and Future Possibilities, *The American Journal of Human Genetics,* March, 1960.

J.A.M.A., June 11, 1960

METHOCARBAMOL IN THE TREATMENT OF BLACK WIDOW SPIDER POISONING

REPORT OF A CASE

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Latrodectus mactans, the black widow spider, is the only spider in the United States capable of producing death in man. While fatalities in arachnidism are rare, the condition is extremely painful due to severe muscular cramps, and untreated patients usually have a protracted convalescence.

A patient admitted to the Louise Obici Memorial Hospital made such a rapid recovery, with symptoms subsiding within 15 minutes after treatment, that it is believed the case should be reported for evaluation of the treatment in future cases of black widow spider poisoning.

The patient, a 26-year-old man, had been bitten on the penis by a black widow spider while he was sitting on an outdoor privy. He experienced the sharp pain of the bite but paid no particular attention to it until pain developed in both lower extremities. Within half an hour the pain was extreme and affected other parts of the body as well. He was taken to the emergency room of the hospital approximately two and one-half hours later. He was in great distress, restless, writhing in agony, and had a grunting, rapid, thoracic type of respiration. Perspiration was profuse. His blood pressure was 160/75 mm. Hg, pulse rate 100 per minute, and temperature 98 F (36.7). He received morphine, 10 mg. intravenously, followed by 100 mg. of hydrocortisone sodium succinate (Solu-Cortef). Pain was only slightly decreased, and the patient was still in great distress. The abdominal wall was completely rigid and boardlike, and the abdomen was somewhat distended. Antivenin had been obtained by them, and 2.5 cc. was given intramuscularly. At the same time 10 cc. of methocarbamol (Robaxin) was administered intravenously. While the methocarbamol was being injected a dramatic change in the patient's condition took place. Relaxation of the tense muscles in the abdomen was felt after injection of the first 5 cc. and became more profound as the injection proceeded. On conclusion of the injection the clinical picture had changed completely. The patient was breathing quietly and no longer complained of pain. Later he received 10 cc. of 10% solution of calcium gluconate intravenously. Other medication consisted of methocarbamol given orally, 1 Gm. every four hours. Two hours after he arrived at the hospital he wanted to return to work and had to be persuaded to stay until next morning for observation. He spent a comfortable day and night in the hospital and was discharged in the morning, having experienced no further pain or discomfort.

Comment

As other drugs were also used, the evaluation of the methocarbamol component was somewhat obscured. However, the noticeable changes—relaxation of abdominal muscles, vanishing of pain, and return of normal respiration—which took place during and immediately after the injection of methocarbamol could hardly have been caused by the morphine or hydrocortisone sodium succinate alone. Any effect of antivenin at this stage was excluded as it could not have brought about an immediate response after an intramuscular injection. Its beneficial effect later on is, of course, most likely, and it must be assumed that the calcium gluconate added to the well-being of the patient. Greer [1] has commented on the treatment of arachnidism with calcium gluconate, and the results were regarded as good when the disability period was four days. Compared to recovery of patients treated before, the recovery of our patient was remarkably quick.

The black widow spider toxin is a neurotoxin and heightens the excitability of the neuromuscular apparatus. Methocarbamol has been shown to have a prolonged blocking activity on multisynaptic reflexes, and it has a marked and prolonged protective action against the cramps of strychnine poisoning.[2] This is a differential diagnostic consideration in a case of arachnidism. Apart from the experimental studies with strychnine poisoning in laboratory animals, the use of methocarbamol in equally intense and generalized muscular cramps, such as in a arachnidism, has apparently not been reported.

Other trials with methocarbamol in the treatment of black widow spider poisoning should be made in order to estimate its real value in this agonizing condition.

Summary

Methocarbamol (Robaxin) was used, in addition to treatment along previously accepted lines, in the treatment of a patient with black widow spider poisoning. Immediate relief was obtained. Further trials with this muscle relaxant should be made.

509 Smith St.

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THROMBOCYTOPENIA AND PURPURA IN PATIENTS RECEIVING CHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE

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Because of their ambidextrous qualities—being useful both as diuretic and as antihypertensive agents—the drugs chlorothiazide and hydrochlorothiazide have, within the past two years, come to enjoy a tremendous use in situations ranging from the treatment of the most severe cases of cardiac insufficiency and essential vascular hypertension to their questionable use in eliminating water from fat persons for purposes of weight reduction. There have been scattered reports in the literature which have mentioned the development of purpura in patients receiving these drugs. In some instances, this purpura has been stated to be accompanied by platelet deficits and in other instances, to be associated with normal platelet counts. Jaffe and Kierland[1] reported two such cases of purpura. In the first case, it was stated that the bleeding and clotting times and other results of hematological tests were normal. In the second case, the platelet count was 94,000 per cubic millimeter. In this latter case, the authors carried out a provocative test by readministering the drug and, after one 500-mg. dose of chlorothiazide (Diuril), the purpura recurred. Lee and associates[2] reported several cases of petechial rash which developed in the course of chlorothiazide therapy and disappeared when use of the drug was discontinued. Two patients with this rash also developed hematuria. These authors mentioned that in two cases the result of the tourniquet test was positive. They also stated that no defects in the blood clotting mechanism were found. Nordquist and associates[3] reported six cases of platelet deficiency associated with chlorothiazide treatment. They believed that three of these cases were proved to be due to chlorothiazide and that the other three were open to question. These authors studied the cases by provocative readministration of the drug, by in vitro tests, and by patch tests. Their in vitro tests included (1) inhibition of clot retraction, (2) immune-precipitate formation, and (3) platelet agglutination and lysis. Zuckerman and Chazan[4] reported a death apparently directly attributable to chlorothiazide therapy, which caused agranulocytosis and thrombocytopenia. Finally, Gesink and Bradford[5] described a case of thrombocytopenic purpura in a patient receiving hydrochlorothiazide and proved the case clinically by readministering the drug, with a resultant return of the full clinical picture of purpura and platelet deficiency.

On the other hand, according to authorities at Merck & Co., Inc.[6] (the manufacturers of the Diuril and HydroDIURIL brands of these drugs), such conditions as described in these articles are indeed rare. The informational brochures from this company do not so much as mention purpura or thrombocytopenia as side-effects. Hydrochlorothiazide is also supplied by CIBA Pharmaceutical Products, Inc., under the brand name Esidrix. This company did not, in its original informational brochures, mention thrombocytopenic purpura, but its latest publications do mention the occurrence of thrombocytopenic purpura as a possibility. Another drug belonging to the same family, flumethiazide, is marketed by E. R. Squibb & Sons, in combination with a rauwolfia compound, as Rautrax. The descriptive literature of this product does not mention thrombocytopenic purpura as a side-effect. Still another drug belonging to the same family, hydroflumethiazide, is supplied by Bristol Laboratories, Inc., as Saluron, and this company does issue in its brochure the precautionary statement that "thrombocytopenia has been reported rarely."

When, in the 14 months prior to the time of writing, four cases of thrombocytopenic purpura in patients receiving these drugs turned up in the routine practice of one man, this circumstance was considered worth description. It will be pointed out in advance that these four cases have not been positively proved to be due to the use of these drugs, since no in vitro tests, patch tests, or provocative readministration of the drug was attempted. Reasonable clinical presumption would, however, implicate these drugs.

Report of Cases

CASE 1.—A 63-year-old woman was first seen on Sept. 5, 1958. She had developed a petechial rash on the arms and legs several days earlier. Her blood pressure was 200/100 mm. Hg. The result of the Rumpel-Leede test was positive. The spleen was not felt. The platelet count was 124,000 per cubic millimeter (normal average being 250,000 to 350,000 per cubic millimeter). The patient had been taking chlorothiazide in doses of 500 mg. once daily for many months prior to my examination—this medication having been prescribed by a physician in

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Member, medical staff, Ball Memorial Hospital.

another state for treatment of the patient's hypertension. The patient had been taking no other medicament. Therapy with chlorothiazide was discontinued on Sept. 5, 1958, and administration of reserpine was started in doses of 0.25 mg. once daily. The petechiae faded within two weeks thereafter and did not recur. A platelet count made on Oct. 16, 1958, was reported as 110,000 per cubic millimeter, and the blood pressure on that date was 165/80 mm. Hg. No further petechiae have occurred to the date of this writing and no further investigation of the blood has been made.

Case 2.—A 66-year-old woman, who was examined on June 24, 1959, stated that during the previous month she had had intermittent temperatures up to 101 F (38.3 C) and that for a few days prior to examination she had noticed petechiae on the lower extremities and lower part of the abdomen. The patient had previously been under my care for many years for chronic cardiac insufficiency and chronic auricular fibrillation associated with rheumatic mitral stenosis. For some years in the past she had been maintained on the usual diuretic program, with the combined use of ammonium chloride, mercurial agents, and dietary salt restriction. In March, 1958, these diuretic measures were discontinued and therapy with chlorothiazide was started and continued during the ensuing 15 months, in doses of 500 mg. daily and occasionally as much as 1,000 mg. daily. At the time of examination in June, 1959, it was found that her platelet count was less than 10,000 per cubic millimeter. The result of the Rumpel-Leede test was positive. The tip of the spleen was palpable. The result of a serum L. E. test was negative, as was that for platelet agglutinins. Therapy with chlorothiazide was discontinued, and the patient was returned to her previous diuretic program of ammonium chloride, mercurial drugs, and dietary salt restriction. By July 6, 1959, her fever had vanished, the petechiae had faded, and the platelet count had returned to 301,000 per cubic millimeter. Within the next few weeks her cardiac insufficiency improved over that of the past months.

Case 3.—A 61-year-old woman, examined on Nov. 5, 1959, was observed to have petechiae over the entire body surface, which had developed within the previous 24 hours. The result of the Rumpel-Leede test on that day was negative. A platelet count was 58,000 per cubic millimeter. The spleen was not felt. Thirteen days previously the patient had been started on therapy with hydrochlorothiazide, in doses of 25 mg. once daily, for treatment of rheumatic mitral stenosis with cardiac insufficiency. Within two days after administration of hydrochlorothiazide was discontinued, the petechiae faded. The patient was then started on treatment with mercurial diuretics. By Nov. 13, 1959, her platelet count had risen to 199,000 per cubic millimeter.

Case 4.—A 79-year-old woman was admitted to the hospital on March 15, 1960, because of bleeding from the rectum. She stated that bleeding from the rectum had been recurrent since 1955. This had been previously determined to come from an ulcerated area in the rectum which had developed after intrauterine radium implantation for cancer. During the two months prior to hospital admission, the rectal bleeding had been increasing in severity and amount. Additionally, the patient had been known to have chronic arteriosclerotic heart disease with cardiac insufficiency. For this she had been treated with various medicaments, including chlorothiazide in doses of up to 1,000 mg. daily during the previous two years. The blood count on admission showed a hematocrit reading of 20%; bleeding and clotting times were normal; prothrombin concentration (Quick) was 76% of control; the platelet count was 112,000 per cubic millimeter. Therapy with chlorothiazide was stopped. Four blood transfusions were given. The hematocrit reading rose to 42% and the platelet count to 222,000 per cubic millimeter. The patient was continued on digitalis therapy and started on ammonium chloride and periodic injections of mercurial diuretics. Bleeding from the rectum ceased entirely, which had not happened in many months. The patient's cardiac insufficiency abated, and her exercise tolerance improved over that of the past months.

Comment

In all four cases discussed, the purpura developed during the administration of chlorothiazide or hydrochlorothiazide, and the condition cleared after discontinuance of therapy with these drugs. In none of these cases had there been any history of previous bleeding tendency or purpura. Hence, it would appear highly probable that the purpura was due to the toxic effect of these drugs. Another possible avenue for clinical thought in such cases is to wonder whether these purpuras may have been simply episodes in the life history of patients having idiopathic thrombocytopenic purpura or systemic lupus erythematosus. In both diseases, drug sensitivity is frequent, perhaps as either a trigger factor or an actual causative factor. In the words of Domz and associates,[7] "The victim of lupus erythematosus has been described as 'first and foremost, an allergic person explosively and furiously responsive.'" The dangerous effects of various drugs in idiopathic thrombocytopenic purpura has been commented on by many. Dameshek[8] has written as follows, "Again, the mode of development of an immunologic reaction in patients eventually developing idiopathic thrombocytopenic purpura is not known.

However, from studies with Sedormid and quinidine thrombocytopenia, it is apparent that these substances, among other chemicals, may act as haptens of various sorts, rendering platelets antigenic and producing highly specific platelet antibodies, which react only in the presence of the drug in question. Antigenicity of platelets in idiopathic thrombocytopenic purpura may conceivably be initiated either through physical alterations of platelets or through the attachment of haptens of various sorts, thus rendering the platelets "unrecognized" by antibody-producing tissues and therefore antigenic. Since the thrombocytopenic purpura of systemic lupus erythematosus is identical in every respect with idiopathic thrombocytopenic purpura, and since apparently typical idiopathic thrombocytopenic purpura may be simply an early manifestation (prodrome) of lupus, it is possible that both idiopathic thrombocytopenia and the thrombocytopenia of systemic lupus erythematosus are based on abnormal immunologic reactions."

Summary

Purpura in association with administration of drugs of the thiazide group has been reported in the literature. I personally have encountered four such cases of thrombocytopenic purpura. Whether these cases of thrombocytopenic purpura represent instances of direct toxic suppression of platelet production, of idiopathic thrombocytopenia, or of systemic lupus triggered or aggravated by these drugs is, to some extent, immaterial. The physician should be guided by the old motto of "Primum non nocere," or "First of all, do no harm," and in administering medicaments of the thiazide group, he should be alert to the possibility of purpura and thrombocytopenia.

2620 W. Jackson St.

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HERNIA THROUGH FORAMEN OF WINSLOW

REPORT OF A CASE AND DISCUSSION

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and
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Hernia through the foramen of Winslow is one of the less common types of internal hernia. Hansmann and Morton [1] found an incidence of 8% in 467 cases of internal hernia collected from the literature.[2] Blandin first described hernia through the foramen of Winslow in 1834. Lavarde and Chevret,[3] in 1949, reported less than 70 cases in the world literature.

The symptoms are usually upper abdominal pain followed by nausea and vomiting. Onset may follow the ingestion of a large meal. A history of previous episodes of upper abdominal pain has been obtained in some patients. Physical findings will vary with the degree of obstruction and the presence or absence of strangulated intestine. An epigastric mass and epigastric fullness have been described.

Roentgenographic evidence of hernia through the foramen of Winslow has been well described. A few instances have been recorded in which a roentgenographic diagnosis was made preoperatively.[4] With herniation of small intestine into the lesser sac, multiple gas and fluid levels that do not conform to the recesses of the lesser peritoneal sac may be visualized. The part of the small intestine proximal to the obstruction may not be dilated because of pressure from the lesser sac on the posterior gastric wall, preventing swallowed air from getting beyond the proximal stomach. With herniation of the right half of the colon, obstruction of the transverse colon at a site corresponding to the foramen of Winslow has been demonstrated on barium enema examination. Findings of an upper gastrointestinal series have demonstrated compression of the stomach by an adjacent gas-filled bowel mass. While the small intestine is most commonly involved, the right colon, including cecum, appendix, ascending colon, hepatic flexure, and proximal transverse colon are involved in a high percentage of cases. The gallbladder[5] and a duodenal diverticulum have been reported as the sole contents of the hernia.

Moynihan and Dobson[6] suggested that at least one of the following abnormalities predisposed to this hernia: (1) a common mesentery for the whole of the intestine; (2) the absence of secondary fusion of the ascending colon to the posterior abdominal wall; (3) an abnormally large foramen of Winslow; or (4) an abnormally long mesentery allowing undue mobility of the intestine.

Report of a Case

A 39-year-old man entered the VA Hospital, Dublin, Ga., complaining of crampy, intermittent, upper abdominal pain of 16 hours' duration. The pain was abrupt in onset and started three hours after the ingestion of a large meal. Nausea and vomiting quickly followed the onset of pain. Vomitus consisted of previously ingested food and contained no blood or feces. This patient had previously been well, but for an episode of hepatitis in 1943 while in military service. There was no history of intolerance to fatty foods. The patient had had infrequent episodes of heart burn, relieved by antacids, of many years' duration. There was no history of episodes similar to the present illness.

On examination, the patient was in acute distress, complaining of sharp, intermittent, upper abdominal pain. Temperature was 97 F (36.11 C), pulse rate 76 per minute, respiration rate 20 per minute, and blood pressure 120/90 mm. Hg. There was no icterus of the skin or sclerae. On examination of the abdomen, there was tenderness in the right upper quadrant and epigastrium and to percussion. There was no spasm and no palpable mass. The abdomen was not distended. Peristalsis was diminished but present. The liver, spleen, and kidneys were not palpable. No incisional scars and no external hernias were present. On rectal examination, there was no mass or tenderness.

Initial laboratory studies showed a white blood cell count of 24,600 per cubic millimeter, with a differential count of 96% neutrophils and 4% lymphocytes. Urinalysis showed no abnormality. The serum amylase level was within normal limits. Plain roentgenographic films of the abdomen, both flat and upright, showed small amounts of air in several loops of small intestine in a "paralytic-ileus" pattern. There was no free air beneath the diaphragm.

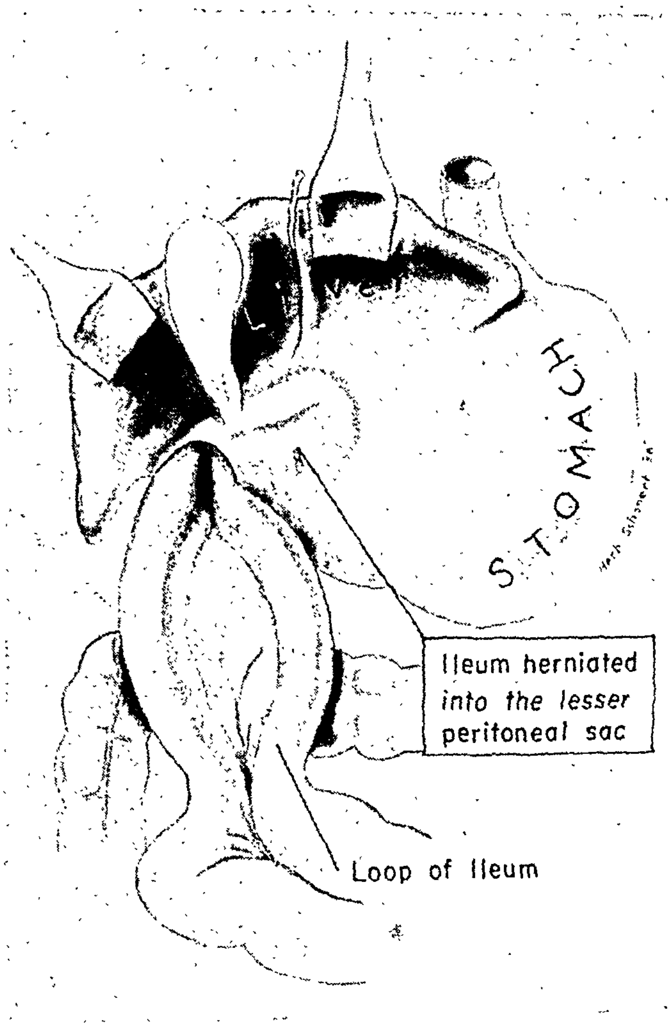

Fig. 1.—Loop of ileum herniated into lesser peritoneal sac.

The tentative diagnosis was acute edematous pancreatitis or acute cholecystitis. A gastric tube was inserted and suction was initiated. Fluids and tetracycline were given intravenously. Atropine was administered subcutaneously every four hours. The tenderness in the right upper quadrant and the epigastrium disappeared after one day of treatment, but abdominal distention appeared and became progressively more marked. Repeat serum amylase determinations were normal. Three days after admission, a serum lipase determination showed a moderately elevated level. On that day, small amounts of bright red blood and black liquid material in small amounts were noted on enema returns. Sigmoidoscopy showed no abnormality to a point 25 cm. above the anus. Barium enema on the fourth day of hospitalization showed no abnormality of the large intestine. Markedly increased amounts of air in the small intestine were also visualized in this study. The dilated small intestine now appeared to have an "obstructive pattern" and to terminate abruptly in the right upper quadrant of the abdomen.

Ninety-six hours after admission, exploration was carried out through an upper right rectusmuscle-splitting incision. On opening into the peritoneal mesenteric border of the small intestine and areas cavity, 500 cc. of free, serosanguinous fluid were found. A 25 cm. segment of distal ileum was herniated through the foramen of Winslow into the lesser peritoneal sac. With gentle traction on the efferent limb of the ileum, the herniated bowel was reduced. There were small areas of necrosis along the anti- of venous thrombosis in its mesentery. Resection of the involved segment with end-to-end anestomosis of the small intestine was performed. The foramen of Winslow was markedly enlarged and readily admitted four fingers. The mesentery of the involved ileum appeared abnormally long. No attempt was made to close this markedly enlarged foramen of Winslow. The patient's postoperative course was uneventful, and he was discharged from the hospital on his 13th postoperative day.

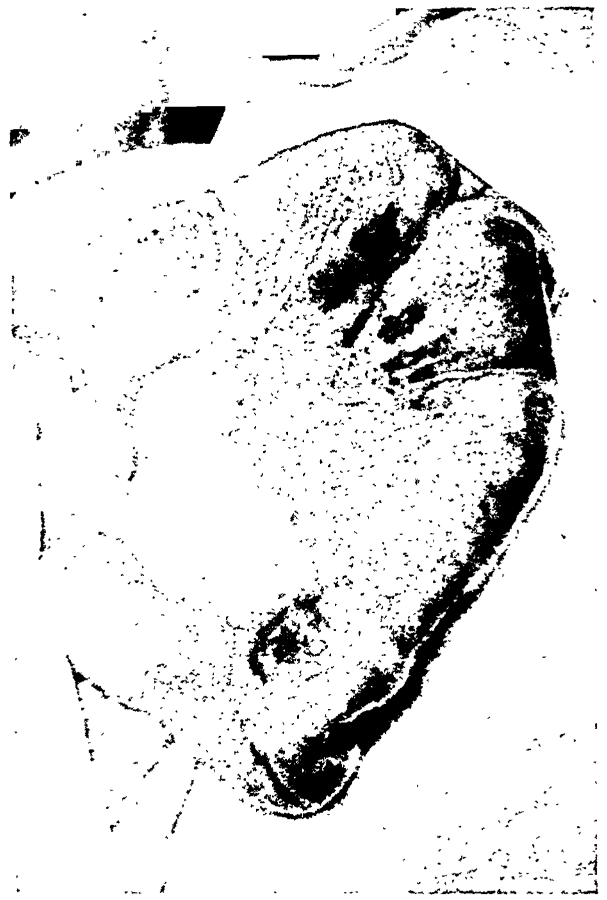

Fig. 2.—Segment of ileum involved in hernia.

Comment

The initial examination of this patient suggested an inflammatory process in the upper abdomen. Findings on physical examination of the abdomen after the initial 24-hour period were those of progressive abdominal distention, with absence of signs of peritoneal irritation. The diagnosis was not made preoperatively on roentgenographic examination. The elevated serum lipase level may have been due to the contact of the strangulated small intestine with the pancreas within the lesser peritoneal sac. The finding of small amounts of bright red discoloration and black liquid material on enema returns suggested the presence of necrotic bowel. However, at that time, this patient had no points of abdominal tenderness.

This patient demonstrated two of the abnormalities listed by Moynihan and Dobson [6] as predisposing to this internal hernia—an abnormally large foramen of Winslow and an abnormally long mesentery allowing undue mobility of the intestine.

Summary

Herniation of distal ileum through the foramen of Winslow is a rare cause of intestinal obstruction. Inspite of delay in operative therapy in the case reported here, a successful result was obtained.

This study was reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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J.A.M.A., June 11, 1960

PNEUMOPERITONEUM AND ANTIBIOTIC THERAPY

TREATMENT OF PYOGENIC LUNG ABSCESS WITH CAVITATION

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Pyogenic lung abscess with cavity formation is seldom mentioned in the literature dealing with chest disorders. Whether lung abscess occurs so infrequently that it is thought unimportant or whether it is considered too benign, self-limited, and responsive to antibiotics to require scientific study is not known. In 1957 Wolcott and Murphy[1] stated that the prognosis and management of lung abscess has changed dramatically in the past 15 years. They reported on 70 patients treated since 1941. In 19 patients treated between 1941 to 1944 with sulfonamide and routine bronchoscopy the mortality was 31.5%. From 1945 to 1951, 29 patients were treated with penicillin given both parenterally and in an aerosol form and supplemented with routine bronchoscopy; five persons, or 17%, died. The third group comprised 27 patients treated from 1951 to 1955. Bronchoscopy was now used only to secure cultural material and for sensitivity studies. The drug of choice was oxytetracycline (Terramycin). Trypsin (Tryptar) in an aerosol form was given to all in this group. The authors attribute the 100% cure obtained to the action of this proteolytic enzyme.

Burch and others[2] reported 15 cases of lung abscess in the mentally ill which occurred after electric shock treatment due to aspiration of oral or gastric contents. They recommended routine bronchoscopic aspiration for sputum cultures and the administration of appropriate antibiotics. Pulmonary resection was required in every case in which bronchoscopy and antibiotics had been delayed longer than three months after the initial aspiration.

Pickar and Ruoff[3] reported 70 patients with lung abscess in April, 1959. Forty-four were treated medically and 26 surgically. On the latter pneumonectomy, lobectomy, segmental resection, thoracoabdominal exploration, and open thoracotomy were performed. There were 12 deaths in the surgically treated series. The five deaths in the medically treated group were due to factors independent of the lung abscess. They conclude that lung abscess is primarily a medical problem. Surgery should be performed only if the patient does not show roentgenographic and clinical improvement, if carcinoma is suspected, or if surgical complications develop. The purpose of this study is to present a simple, effective method of treating early acute pyogenic lung abscess with cavitation by the combined use of antibiotics and pneumoperitoneum.

Report of Cases

CASE 1.—A 36-year-old woman developed catarrhal and constitutional symptoms of an acute virus infection on Feb. 2, 1958. Productive cough was associated with low-grade fever, chills, sweats, and fatigue. These symptoms were unresponsive to a wide range of antibiotics and persisted until April 10, when the patient developed a severe pleuritic pain on the left side. On April 14 the pain shifted to the right side of the chest. The patient appeared to have a toxic condition and had a severe cough with yellow purulent sputum. Her temperature was 100.6 F (38.6 C). Examination of the chest was unrevealing. The roentgenogram taken April 14 showed a pneumonic infiltration in the right upper lobe containing several small cavities.

The patient was hospitalized. She was started on therapy with sterile penicillin-dihydrostreptomycin for suspension (Dicrysticin) given intramuscularly, tetracycline oleandomycin (Signemycin) given orally, and oxytetracycline given intravenously. Sputum cultures revealed hemolytic Staphylococcus aureus and alpha hemolytic streptococci. Intradermal tuberculin skin tests and sputum studies showed negative results for a tubercular infection. Air was injected into the peritoneal cavity in the following amounts: 1,000 cc. on April 14, 1,000 cc. on April 15, and 800 cc. on April 16. The roentgenogram taken on April 17 showed a cushion pneumoperitoneum. The area of pneumonitis was smaller, and the abscess cavity appeared more defined. On that day the patient became afebrile, and her cough and expectoration disappeared. The roentgenogram taken on April 21 showed the continued presence of the pneumoperitoneum. The right hemidiaphragm of the diseased lung remained elevated in the same position, whereas the left was lower and was separated from the spleen by a small ribbon of

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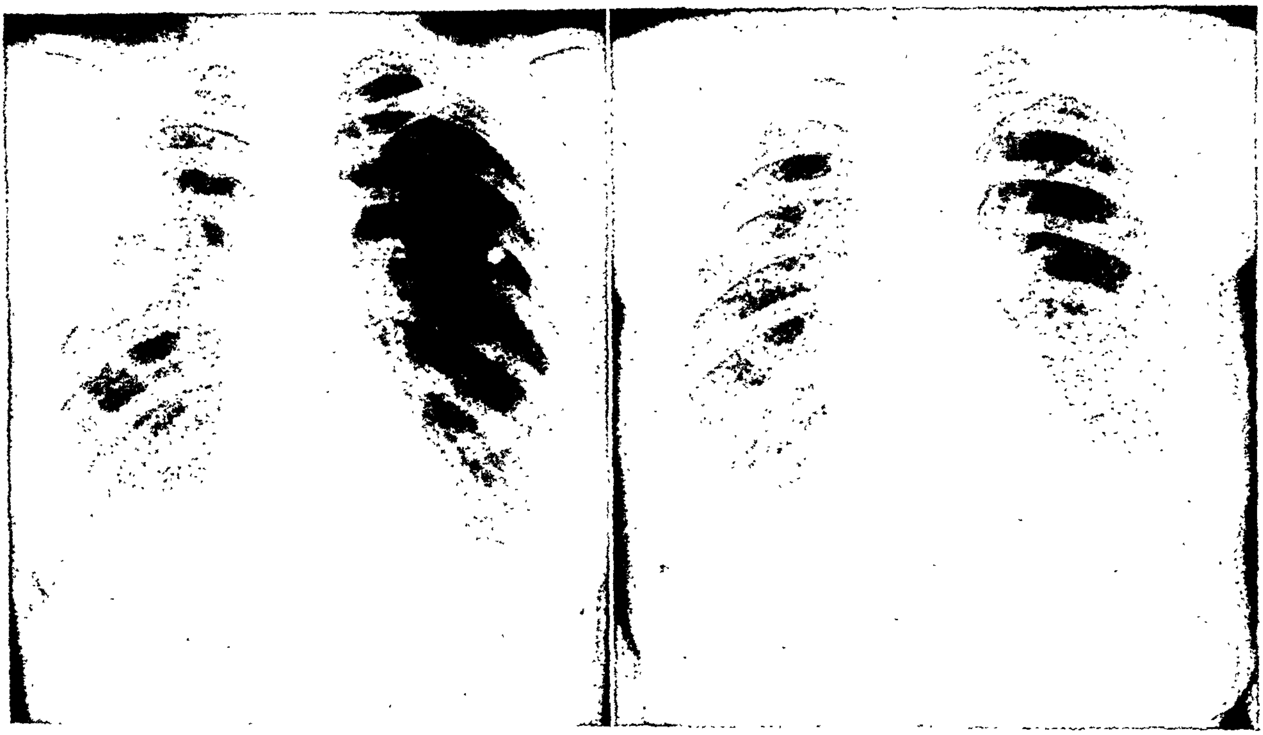
From the Medical Department of St. Anthony Hospital.

air. The pneumonitis continued in the phase of absorption, and the cavity was now difficult to outline. The patient was discharged, clinically well, on April 26, after a hospital stay of 12 days. The roentgenogram taken on May 16 showed complete disappearance of the pneumonitis and abscess cavity with restitio integrum of the lung.

CASE 2.—A 58-year-old woman developed an acute virus infection on March 12, 1959. She had a severe productive cough, daily temperature as high as 102 F (38.9 C), chills, night sweats, and pain in the right side of the chest, and she was extremely fatigued. For the next three weeks she was treated inadequately with short courses of tetracycline hydrochloride (Achromycin) and an occasional injection of penicillin, which resulted in a large gluteal abscess. Examination revealed roentgenographic findings (see figure, *left*) of pneumonitis in the right upper lobe with a cavity in the posterior segment of that lobe. When she was admitted to the hospital on April 1, she was acutely ill and mentally confused and had a toxic condition. Her temperature was 102 F (38.9 C). Physical examination revealed dulness in the right lung from the first rib to the third rib anteriorly with vesiculobronchial breath sounds, increased whispered and spoken voice sounds, and numerous subcrepitant rales in that area. Sputum cultures revealed Staphylococcus albus. Because of her poor general health, her condition was maintained on chloramphenicol (Chloromycetin) given orally and oxytetracycline given intravenously until April 8, when treatment with air injected into the peritoneal cavity was begun. On April 8, 450 cc. of air was injected; on April 9, 650 cc.; on April 11, 450 cc.; on April 12, 800 cc.; and on April 16, 500 cc.

After the third injection the chest pain disappeared and the patient's temperature decreased to 99 F (37.2 C). A roentgenogram taken on April 16 showed a pneumoperitoneum with the right diaphragm slightly higher than the left. The pneumonic exudate showed clearing, and the cavity appeared smaller and displaced upward. She was discharged, considerably improved, on April 19, after a hospital stay of 18 days. The roentgenogram taken on April 24 showed the continued presence of pneumoperitoneum, although no injection had been given since April 16. There was evidence of further improvement. The pneumoperitoneum was still present when fluoroscopy was performed on



Patient in case 2 before and after treatment. *Left*, soft-appearing pneumonitis of right upper lobe extends from first rib anteriorly to below fourth rib anteriorly with flat-based cavity measuring 6 cm. in its greatest diameter in center of pneumonitis. Right costophrenic angle is displaced downward, and inner half of right diaphragm is very irregular. *Right*, there is complete absorption of pneumoperitoneum, and pneumonitis and cavity can no longer be seen. Interlobar fissure is thickened with small fibrotic residue in previous morbid process.

May 15, one month after the last refill. The roentgenogram taken on May 29 (see figure, *right*) showed complete absorption of the air in the peritoneal cavity and complete disappearance of the pneumonitis and the large abscess cavity. A small fibrotic residue in the area of the previous morbid process could be seen. The patient made a splendid clinical recovery.

Comment

Viral pneumonitis has a high incidence in the morbidity of acute inflammatory processes of the lungs. The disease is relatively benign, self-limited, and responsive to the present-day broad-spectrum antibiotics. Patients usually make a complete recovery without complications or sequelae. In certain patients, however, suppuration of the pneumonitis, with abscess and pyogenic cavity formation, occurs instead of resolution. The pathological picture may merely be that of multiple thin-walled small cavities, as in case 1, or that of a large flat-based cavity with a fluid level, as in case 2. The former may be still adequately treated with antibiotics, while the latter may not prove so responsive, especially if the cavity wall becomes thick and fibrotic. In such a case surgical resection becomes a possibility. With that in mind, it was felt that the simple expedient of injecting air into the peritoneal cavity might be a nonsurgical approach to the obliteration of early pyogenic lung abscess cavities.

Cieza and others,[4] in 1938, described one case of lung abscess closed by the injection of air into the peritoneal cavity. This has remained the only such published report to date. Pneumoperitoneum was used for a short while in the treatment of certain cases of pulmonary tuberculosis, only to be replaced by specific drugs and chest surgery. Today it is used rarely and sporadically. In experienced hands, pneumoperitoneum is a simple procedure. If it is done carefully by one who understands the technique and the fluctuation of the manometer of the pneumothorax machine, complications are seldom encountered.

Lung abscess has a predilection for the right lung, especially the upper lobe. In Pickar and Ruoff's 70 patients, 41, or 58.6%, of the abscesses were in the upper lobe. There were 15, or 21%, in the right lower lobe. Ten, or 14%, were each in the left upper and lower lobes. The question may arise as to whether the technique of pneumoperitoneum has any value in upper lobe morbid processes. The pull of the diaphragm is reflected most intensely beneath the clavicles. For that reason it has been shown that tuberculous cavities beneath the clavicle often disappear after phrenic nerve surgery or pneumoperitoneum has been made. The air has a tendency to accumulate more readily beneath the diaphragm of the diseased lung and to absorb more slowly than from under the contralateral diaphragm. The elevation of the diaphragm reduces the volume of the lung, and with the elevation there is relaxation and reduction of tension of the morbid process, which permits healing to take place. Free drainage with evacuation of the cavity is facilitated without the use of bronchoscopy.

The abscess cavity is usually subpleurally located with a pleuropulmonary reaction that can produce severe persistent pleuritic pain. The elevation of the diaphragm with relaxation of tension of the diseased lung can be a factor in causing the pain to subside and disappear. Furthermore, the mechanical action of pneumoperitoneum is a force in minimizing the sequelae of bronchitis and bronchiectasis that may result if the abscessed cavity becomes chronic.

Although the specific organism is identified and cultured and sensitivity tests are performed, the patient may be drug resistant or allergic to the specific agent. The mechanical action of pneumoperitoneum may aid the body in its inherent immunobiological response in patients to whom antibiotics cannot be given. It is to be emphasized that if this treatment is to be successful, it should be instituted early, before the cavity becomes thick-walled, chronic, and fibrotic. Only a few injections are needed to cause and to maintain the desired therapeutic result. A cushion of air under the diaphragm is sufficient to produce an anatomical rise and response. The treatment is reversible in that the diaphragms return to their previous position and function after the air is absorbed with cessation of refills.

Summary and Conclusions

It is felt that the morbidity of pyogenic lung abscess with cavity formation is higher than mentioned in the literature. The technique of pneumoperitoneum should particularly be considered if there is any contraindication to chemotherapy, particularly drug resistance or allergy. The patient is thus presented with a mechanical objective approach to supplement his inherent immunobiological reaction.

Pneumoperitoneum should be considered before surgery is contemplated. The exception is a pyogenic lung abscess cavity due to an inaccessible foreign body or to carcinoma, in which case surgical intervention is the only solution. As was shown, the predilection for lung abscess with resultant cavitation in an upper lobe is no deterrent to injection of air into the peritoneal cavity in patients in whom it is selectively effective. When instituted early, it will cause the concomitant pneumonitis to absorb and the cavity to disappear.

Pneumoperitoneum is a factor in shortening the hospital stay and in making recovery more complete without the sequelae of possible bronchitis and bronchiectasis. Only a small cushion of subdiaphragmatic air is sufficient to produce the desired clinical and radiographic response. Further rise of the diaphragm can be accomplished, if necessary, by merely increasing the quantity of the refill. It has been shown that the diaphragm remains elevated for a sufficient length of time without the need of repeated injections, thus maintaining its therapeutic effectiveness during the acute phase of the abscess cavity.

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SIMPLE METHOD FOR THE MEASUREMENT OF ALVEOLAR CARBON DIOXIDE

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and
Charlotte R. Colp, M.D., Boston

Measurement of alveolar carbon dioxide tension is important in the diagnosis and care of patients with pulmonary disease, during anesthesia, in coma, and in other conditions with increased or depressed alveolar ventilation. A previous communication[1] described a simple, accurate, inexpensive apparatus for the bedside measurement of alveolar carbon dioxide tension. The present report deals with the clinical application of this method to eucapnic, hypercapnic, and hypocapnic subjects. The results are compared with simultaneous measurement of arterial blood carbon dioxide tension, and a method is outlined for use of the apparatus in patients in coma or unable to produce an adequate alveolar sample on a single breath.

Materials and Methods

Nineteen patients referred for pulmonary function studies and presenting a variety of cardiopulmonary diseases were studied. Simultaneous measurements were made of the carbon dioxide tension of their arterial blood and end-expired or rebreathing gas samples, or both.

The principle of this method is simply that, with the absorption of carbon dioxide by 2*N* NaOH (sodium hydroxide) in an air-tight chamber, a negative pressure is produced in relation to atmospheric pressure. Since exhaled air is saturated with water vapor and 2*N* NaOH has a similar vapor pressure, any error due to absorption of water vapor will be minimized. The carbon dioxide tension of the alveolar gas sample ($P_{A_{CO_2}}$) is recorded by the negative pressure deflection of an aneroid manometer connected to the chamber. The results obtained with this method have been previously compared to analyses performed with a micro Scholander apparatus.[1] Fifteen serial determinations on aliquots of a known gas sample (P_{CO_2}) were as follows: 50, 50, 50, 51, 46, 51, 51, 50, 50, 50, 50, 50, 51, 50, and 50, with a mean of 50 mm. Hg and a standard deviation of ±1.14.

To measure the carbon dioxide tension of an end-expired sample, the subject exhales maximally through two J valves set parallel at the entrance and exit of the air-tight chamber. At the end of the expiratory effort, a sample of alveolar gas will be collected in the reaction chamber, provided the expiratory volume has been large enough (about 1,100 ml.) to wash out the respiratory dead space

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of the subject and the chamber. If the expired volume is less than 1,100 ml., cooperation of the patient is required in exhaling multiple small portions of end-expired air through the chamber on successive breaths. At the conclusion of expiration the mouthpiece valve is quickly closed. The distal valve is also closed to prevent leakage of the absorbing fluid. A short temperature equilibration (one to two minutes) is then required. A low negative pressure may be produced because of contraction of cooling gases and should be substracted from the final result. The sealed glass ampul of 2*N* NaOH is then shattered against a metal pin inside the chamber and the carbon dioxide is absorbed until equilibrium occurs (one to two minutes) fig. 1, *above* and *below*).

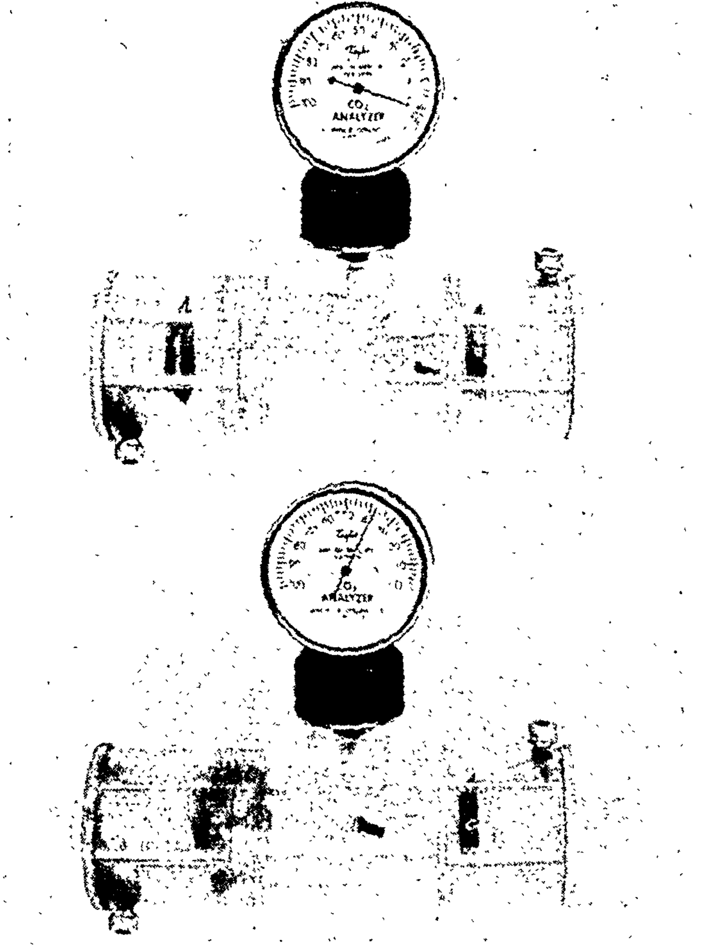

Fig. 1.—*Above*, lucite chamber shown with valves in open position, ampul intact, and no pressure registered on vacuum gauge. *Below*, air sample has been expired through chamber, valves are sealed in closed position, ampul is shattered, and equilibrium pressure of 38 mm. Hg is attained.

The instrument described may be easily modified into a rebreathing apparatus for use in comatose, uncooperative, or anesthetized subjects, or those with a small vital capacity (see fig. 2). It has been shown that in rebreathing a suitable gas mixture, the carbon dioxide tension of the gas mixture and the lung volume will equilibrate with that of mixed venous blood (see fig. 3).[2] Since the difference between arterial and mixed venous carbon dioxide pressure (P_{CO_2}) has been observed to be relatively constant, the arterial P_{CO_2} can be approximated by empirically subtracting 6 mm. Hg as described by Collier.[3] For most subjects rebreathing 1 liter of 7.5% carbon dioxide in oxygen will give good results. If the carbon dioxide tension is observed to be greater than 50 mm. Hg, measurements using 10% carbon dioxide in oxygen should be made. Determinations should be performed at 30, 40, and 50 seconds of rebreathing. Rebreathing should be carried out with nares obstructed and care taken to prevent leaks in the system. A mouthpiece or mask of small dead space will insure a tight fit in uncooperative patients. At the end of the rebreathing period, the cylinders are quickly closed and the analysis is carried out as described above.

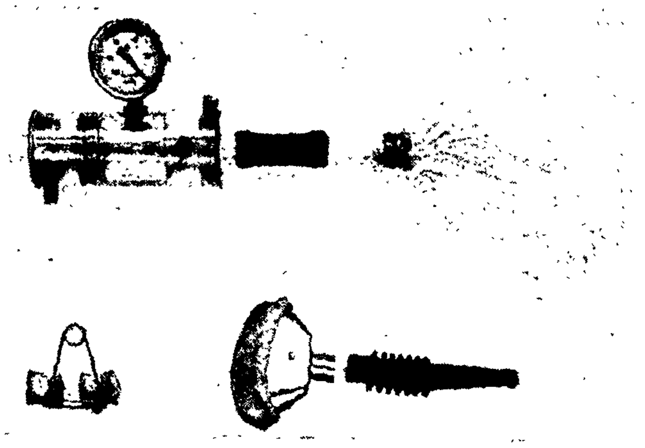

Fig. 2.—Apparatus used for rebreathing measurements. Rebreathed air passes through large pores adjacent to sealed ends of cylinders. Adaptations may be useful in uncooperative or comatose patients or those with tracheostomy.

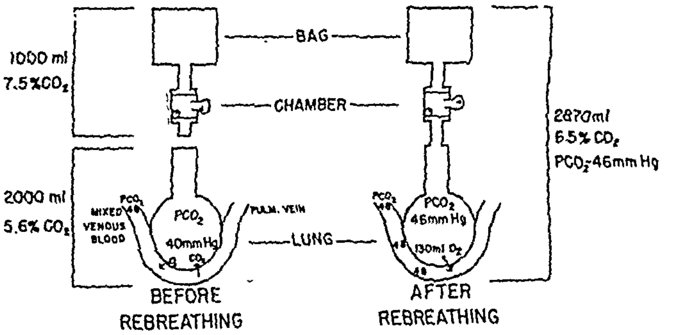

Fig. 3.—Simplified scheme of rebreathing technique. After short period of rebreathing, equilibration will occur in bag-chamber-lung system. Although oxygen is absorbed by blood in pulmonary capillaries, equilibration of carbon dioxide occurs between mixed venous blood and alveolar air. Changes due to Haldane effect, dead space, temperature, tissue absorption of carbon dioxide, and recirculation are ignored in this illustration.

For purposes of comparison, brachial artery blood was obtained in the patients studied. Arterial blood oxygen content, capacity, and carbon dioxide content was measured in the Van Slyke-Neill apparatus.[4] The pH was measured with a glass electrode at 37 C. Arterial P_{CO_2} was obtained by applying the line chart of Van Slyke and Sendroy to the pH and plasma carbon dioxide content.

Results

This method of measuring carbon dioxide tension of end-expired or rebreathed air showed excellent correlation with carbon dioxide tension measured by arterial blood analysis (fig. 4 and table). In patients in coma or in those with small expiratory volumes, it was not always possible to obtain adequate end-expired samples, whereas application of the rebreathing technique to the same subjects yielded accurate results (patients 4, 5, 17, and 18 in table). The following cases illustrate a few applications of this apparatus to clinical problems of therapeutic management, evaluation of operative risk, and differential diagnosis.

Report of Cases

Case 1.—A 57-year-old man with a five-year history of asthma was hospitalized for reduction of steroid dosage. After several days of intermittent therapy with oxygen by mask, he exhibited severe cyanosis and an alveolar P_{CO_2} of 81 mm. Hg was recorded. Limitation of oxygen therapy was advised and a fall in P_{CO_2} to 56 mm. Hg occurred in 24 hours. Pulmonary function studies were consistent with severe bronchospasm and emphysema.

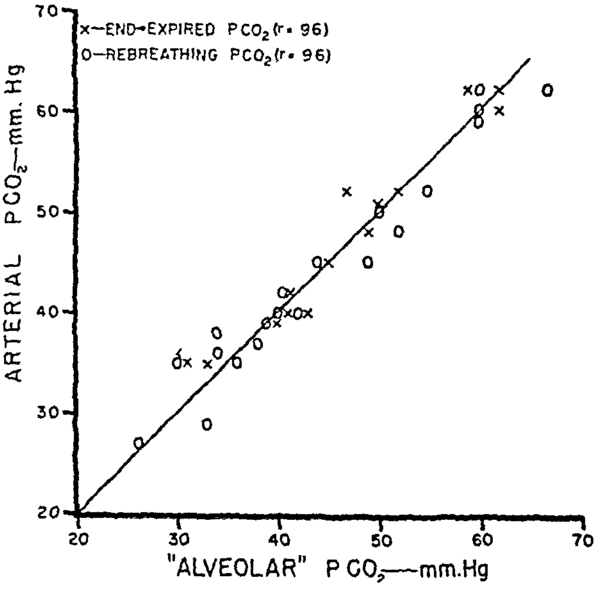

Fig. 4.—Results comparing end-expired and rebreathing P_{CO_2} with P_{CO_2} measured in arterial blood.

Case 2.—A 54-year-old man was admitted for evaluation of pulmonary function prior to pneumonectomy for a tumor of the right main bronchus with right upper lobe involvement. Alveolar P_{CO_2} measured in the chamber was 40 mm. Hg, and, although collateral studies indicated mild obstruction to air flow not reversed by administration of bronchodilators, surgery was performed and the patient withstood the procedure satisfactorily.

Comparison of Rebreathing, End-expired, and Arterial P_{CO_2} Measurements

Patient, No.	Rebreathing P_{CO_2}-6 Mm. Hg	End-expired P_{CO_2} Mm. Hg	Arterial Blood P_{CO_2} Mm. Hg	Diagnosis Given
1*	50	50	50	Emphysema
	42	41	41	
2	40	40	41	Normal
3	39	40	39	Normal
4	33	...	29	Cerebrovascular accident, coma
5	38	...	37	Cerebrovascular accident, coma
6	34	...	38	Pulmonary fibrosis
7	26	...	27	Congenital heart disease
8	36	31	35	Atrial septal defect
9	30	33	35	? Pulmonary emboli
10*	67	62	62	Emphysema
	55	52	52	
11	...	43	40	Aortic stenosis, congestive heart failure
12	52	48	49	Pneumonia, emphysema
13	34	30	36	Pulmonary emboli
14	...	47	52	Emphysema
15	49	45	45	Kyphoscoliosis
16	59	60	62	Emphysema
17	30	...	30	Pneumonia, tracheostomy
18*	40	...	37	Hypoventilation, tracheostomy
	42	...	40	? Cerebrovascular accident
19	41	41	42	Sickle cell anemia, pulmonary infarcts

* Studied on two occasions.

Case 3.—A 53-year-old man had been under psychiatric treatment for one year for psychogenic dyspnea. His alveolar P_{CO_2}, however, was 51 mm. Hg, and additional studies revealed severe bronchoconstriction unresponsive to therapy with bronchodilator drugs.

Case 4.—A 48-year-old woman was admitted with moderately severe dyspnea and chest pain. Chest x-ray revealed normal findings. A serum carbon dioxide combining power (venous) was 19 mEq. and metabolic acidosis was suspected. However, alveolar P_{CO_2} was 22 mm. Hg, and a subsequent arterial blood pH of 7.54 confirmed the diagnosis of respiratory alkalosis.

Comment

Our studies indicate that the method and apparatus herein described provide a means for the rapid, simple, inexpensive, and accurate measurement of the clinically important parameter of alveolar carbon dioxide tension.

The excellent correlation of alveolar P_{CO_2} measured after end-expiration or rebreathing with arterial P_{CO_2} is in agreement with other reports of studies in which different methods of detecting carbon dioxide in an alveolar gas sample were used.[6] The results obtained in the emphysematous patients require comment, since it might be expected that an end-expired gas sample would not be representative of mean alveolar P_{CO_2}. However, the 60 ml. of gas in the reaction chamber is representative of a large portion of alveolar air, and it is probable that this method gives a closer approximation to mean alveolar P_{CO_2} in emphysematous subjects than other methods which sample a smaller portion of expired gas.[7]

Previous experimentation has demonstrated that the P_{CO_2} in a lung-bag system after a suitable period of rebreathing will accurately reflect the mixed venous carbon dioxide tension. While Hackney and colleagues [6a] observed that the arteriovenous carbon dioxide difference may be as great as 12 mm. Hg in some persons, the empirical subtraction of 6 mm. Hg appears to be adequate for clinical measurements.

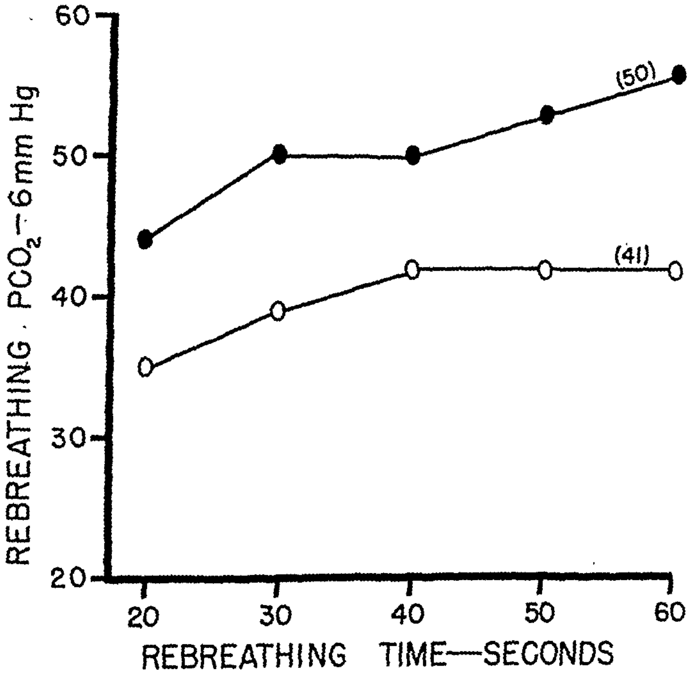

Fig. 5.—P_{CO_2}—6 mm. Hg after various periods of rebreathing in normal subject (*open circles*) and patient with emphysema (*closed circles*). Figures in parentheses are carbon dioxide tensions measured in arterial blood.

The rebreathing periods of 30, 40, and 50 seconds were selected after observation of the results in normal subjects and in patients with pulmonary disease. While many normal subjects will reach a constant level of carbon dioxide tension in the bag-chamber-lung system within 20 seconds, some patients with pulmonary emphysema did not reach plateau pressure levels until 30 seconds (fig. 5). Although recirculation may produce elevations during prolonged rebreathing periods, the error seems to be of small magnitude [2c] and acceptable for clinical purposes. Inconstancy of the results at 30, 40, and 50 seconds, i. e., absence of a plateau, may indicate a leak in the system, hypoventilation, or a marked degree of recirculation.

Summary

An instrument for rapid and accurate detection of alveolar carbon dioxide tension has been described. The results obtained on samples of end-expired and rebreathing air have been compared to simultaneously obtained samples of arterial blood analyzed for carbon dioxide tension. The apparatus has been most helpful in establishing the presence of carbon dioxide retention, in clarification of problems of acid-base balance, and in following the effects of therapy.

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Mrs. Isabel Kogos gave technical help and Earl C. Nickles and R. Mori of Warren Collins Co. cooperated in the development of the apparatus.

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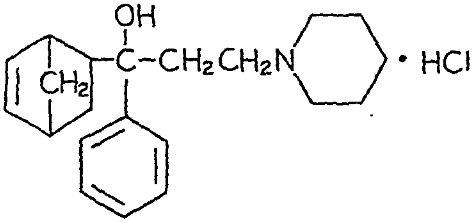
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. Kautz, M.D., *Secretary.*

Biperiden Hydrochloride (Akineton Hydrochloride).—α-(Bicyclo[2.2.1]hept-5-en-2-yl)-α-phenyl-1-piperidinepropanol hydrochloride.—The structural formula of biperiden hydrochloride may be represented as follows:



Actions and Uses.—Biperiden hydrochloride, like trihexyphenidyl, procyclidine, and cycrimine hydrochloride, to which it is chemically related, is an anticholinergic agent employed in the symptomatic management of paralysis agitans (Parkinson's disease). The available evidence suggests that it closely resembles the older drugs in this group in range of usefulness, effectiveness, and side-effects. Thus, in patients responding favorably, it appears to effect a reduction in rigidity, to suppress excessive salivation and sweating, to improve gait and the ability for self-care, and to reduce the incidence and severity of oculogyric crises. There is little effect on tremor and only questionable improvement in the patient's mental outlook. It must be pointed out, moreover, that biperiden hydrochloride has not been adequately studied in the clinic and that the effects described are largely clinical impressions not yet confirmed by carefully planned experimentation. There is no evidence that the drug is superior to other antiparkinsonian agents. It seems to be less effective in the arteriosclerotic form of the disease than in the postencephalitic or idiopathic forms or in drug-induced parkinsonism-like syndromes. There is as yet no known contraindication to its use in conjunction with other antiparkinsonian drugs.

Biperiden hydrochloride also has had limited trial in the management of the spasticity associated with hemiplegia, injuries of the spinal cord, cerebral palsy, multiple sclerosis, and other disorders involving the pyramidal tract. The data supporting its usefulness in these conditions are, at best, only suggestive. Few patients seem to experience more than minimal improvement from its use; in spastic hemiplegia, many patients given this therapy become weaker, with consequent impairment in the ability to move or walk. Purported beneficial effects include diminution of muscular spasm and facilitation of physiotherapy in patients with cerebral palsy and suppression of hyperhidrosis in patients with paraplegia due to spinal cord injuries.

Pharmacological studies indicate that biperiden hydrochloride has the spasmolytic and antisecretory actions typical of anticholinergic agents. It is one twenty-fifth as active as atropine in antagonizing the spasmogenic effects of cholinergic agents on the intestine, about one-third as active as atropine in inhibiting salivation, and about one-sixth as potent as a mydriatic agent. The drug antagonizes the effects of nicotine on the blood pressure and nictitating membrane and prevents nicotine convulsions.

Side-effects include dryness of the mouth, blurred vision, dizziness, and gastric irritation. Minor side reactions can be minimized by proper adjustment of dosage and often become less troublesome with continued use of the drug. The drug seems to be comparatively free from untoward psychic effects, but restlessness and mental confusion occasionally occur; transient psychotic reactions have also been reported. Urinary retention and hematuria (each reported in a single case) have followed the administration of the drug to children. Like other atropine-like agents, biperiden hydrochloride should be used with great caution, if at all, in the presence of glaucoma or prostatic hypertrophy.

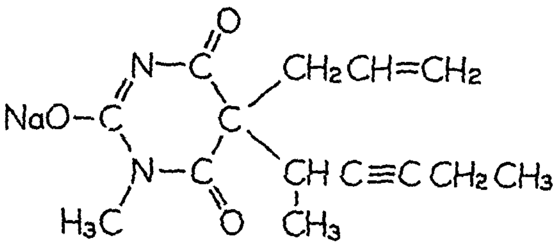
Dosage.—Biperiden hydrochloride is administered orally. The dose must be adjusted in accordance with the needs and tolerance of each patient; 2 mg. three or four times daily is suggested as an average requirement. Untoward effects are sometimes avoided by giving very small doses initially and gradually increasing the dose as needed. Gastric irritation is less troublesome if the drug is given during or after meals.

Preparations.—tablets 2 mg.

Year of introduction: 1959.

Knoll Pharmaceutical Company cooperated by furnishing scientific data to aid in the evaluation of biperiden hydrochloride.

Methohexital Sodium (Brevital Sodium).—Sodium *a-dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)barbiturate.—The structural formula of methohexital sodium may be represented as follows:



Actions and Uses.—Methohexital sodium, an ultrashort-acting barbiturate, is used intravenously as a general anesthetic agent. It is similar in action to thiopental sodium and related ultrashort-acting barbituric acid derivatives. However, it differs from thiopental in a number of respects. Methohexital is more potent than thiopental and consequently produces the same degree of anesthesia with smaller doses. However, much of the initial dose of thiopental apparently is absorbed by the fatty tissues and is later released back into the circulation, which permits smaller maintenance dosage near the end of anesthesia. On the other hand, methohexital, which is not absorbed by fatty tissue to the same degree, requires constant dosage to maintain an even level of anesthesia. Thus, the total dose of methohexital approaches that of thiopental after a period of three hours of anesthesia. Induction of anesthesia with methohexital is as rapid as it is with thiopental, but recovery from anesthesia is more rapid with methohexital than with thiopental.

Methohexital sodium may be used for the induction of general anesthesia or as the sole anesthetic agent for minor operative procedures which do not require muscle relaxation. It can be given by intermittent or by continuous drip techniques. When administered intermittently, more frequent injection is necessary with methohexital than it is with the thiobarbiturates. This is true especially when the drug is used as the sole anesthetic agent because of the rapid metabolism of this agent. For operations requiring muscle relaxation, methohexital must be supplemented by a gas anesthetic such as nitrous oxide plus oxygen. When methohexital is administered along with a gas anesthetic and a muscle relaxant, the resultant anesthesia is smoother and can be maintained with smaller doses of each agent. On the basis of data thus far available, it would appear that the principal advantage of methohexital lies in the patient's relatively short recovery period following cessation of its administration. The blood concentration of methohexital in experimental animals three hours after cessation of anesthesia is approximately 40% of the concentration in the blood at the end of the third hour of anesthesia; under the same conditions, the blood level of thiopental is 80%.

Side-Effects.—Methohexital sodium administration may be associated with muscle twitching or more severe convulsive movements due to motor excitation, sneezing, coughing, hiccuping, laryngospasm, and respiratory stridor. These may appear when induction of anesthesia is too rapid or, conversely, when the induction dose is inadequate and/or given too slowly for the patient to reach the proper depth of anesthesia. Respiratory depression and/or apnea, dangers inherent in the use of any barbiturate given intravenously, may occur. Therefore, alertness is essential to avoid the effects of overdosage. Postanesthetic shivering, associated with a marked fall in body temperature, has been observed in a few cases. Administration of this agent should be performed only by individuals well versed in the use of anesthetics given intravenously; facilities for providing oxygen and for insuring a patent airway and adequate respiration should be available at all times. As with other intravenously administered barbiturates, methohexital should be used cautiously in patients with respiratory obstruction, asthma, severe hypotension or hypertension, myocardial disease, congestive heart failure, anemia, and extreme obesity. Although the avenues of detoxication and excretion of methohexital have not yet been elucidated, the drug is probably contraindicated, as are other barbiturates, in patients with severe hepatic dysfunction.

Methohexital may be used with any of the usual preanesthetic medicaments. Although it does not cause muscle relaxation, the drug is compatible with any of the skeletal muscle relaxants and may be given concomitantly.

Dosage.—Methohexital sodium is administered only by the intravenous route. The techniques, procedures, and precautions for its administration are the same as with other ultrashort-acting barbiturates used as general anesthetics.

For the induction of anesthesia, 70 to 100 mg. (7 to 10 cc. of a 1% solution) will usually suffice. For intermittent administration in the maintenance of general anesthesia (as supplemented by a gaseous anesthetic plus oxygen), small doses ranging from 20 to 40 mg. (2 to 4 cc. of a 1% solution) may be injected at intervals governed by the usual signs relating to the depth of anesthesia. A 1% solution also may be used for administration by continuous intravenous drip.

Preparations.—powder (injection) 500 mg. and 2.5 Gm.

Year of introduction: 1960.

Eli Lilly and Company cooperated by furnishing scientific data to aid in the evaluation of methohexital sodium.

Ophthalmic Use Of Tetrahydrozoline Hydrochloride (Visine).

Tetrahydrozoline hydrochloride is a potent sympathomimetic agent which was described previously for intranasal instillation in the symptomatic treatment of inflammatory hyperemia and edema of the nasal mucosa; for this purpose, it is marketed under the trade name Tyzine Hydrochloride. (See the monograph on tetrahydrozoline hydrochloride in New and Nonofficial Drugs.) The Council subsequently has evaluated the usefulness and safety of the drug for use as an ophthalmic decongestant. Preparations intended for use in the eye are marketed on an over-the-counter basis under the trade name Visine.

When instilled into the conjunctival sac, solutions of tetrahydrozoline cause vasoconstriction of peripheral vessels. As measured by blanching of hyperemic conjunctiva, the onset of vasoconstriction is apparent within several minutes and persists for about four hours. Clinical reports indicate that the drug is useful as an ophthalmic decongestant for the symptomatic relief of conjunctival edema and hyperemia secondary to ocular allergies, minor irritations, and so-called nonspecific or catarrhal conjunctivitis. Beneficial effects include amelioration of burning, irritation, pruritus, soreness, and excessive lacrimation. Rebound vasodilation and congestion have not been reported. In approximately 2% of patients, a transient burning or stinging sensation is experienced when the drug is instilled into the eye; there is no evidence that it induces sensitization.

Ophthalmic solutions of tetrahydrozoline hydrochloride do not affect reaction to light or accommodation. On the basis of its other sympathomimetic properties, however, some degree of mydriasis is to be expected. Thus, in experimental animals, it is possible to produce a slight pupillary dilation. One clinical investigator also reported instances of a dilation of 0.5 mm. in the pupils of three of eight patients studied. However, the majority of clinical observers, using the drug in a large number of patients with and without glaucoma, have been unable to detect any significant increases in pupillary size or intraocular pressure. Hence, the likelihood of inducing acute glaucoma in patients in whom the iridocorneal angle is narrow seems quite remote. Pending conclusive confirmation of this fact, however, caution is enjoined against use of tetrahydrozoline in any person with serious eye diseases such as glaucoma. This warning, carried on the label of ophthalmic solutions, is particularly appropriate since the drug can be obtained without a physician's prescription.

For ophthalmic use, two or three drops of a 0.05% solution of tetrahydrozoline hydrochloride is placed in each eye two or three times daily.

The Council voted to expand the monograph on tetrahydrozoline hydrochloride in New and Nonofficial Drugs to include the foregoing comments concerning its proposed use as an ophthalmic decongestant.

Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., cooperated by furnishing scientific data to aid in the evaluation of the ophthalmic use of tetrahydrozoline hydrochloride.

THE POSSIBILITY OF ERADICATING TUBERCULOSIS.—Since the frequency of tuberculin reactors among persons who are now twenty years of age is the cumulative result of infections which have occurred at sometime during the last twenty years, the total prevalence of 5 per cent found in these young men corresponds to an average infection rate of 2 per 1,000 per year from 1938 to 1959. However, as there are many indications that the infection rate has not been constant during these years but has been declining rapidly, the infection rate throughout large parts of the country must now be less than 1 per 1,000 per year. The consequences of these and other studies now in progress can be expected to open the way for programs aimed at the final eradication of tuberculosis. It is clear that tuberculous infection is not the only cause of tuberculin sensitivity. The evidence from both experimental animals and human patients with clinical disease shows that tuberculin sensitivity may be caused by infection with other types of mycobacteria, just as it may be caused by virulent tuberculous infection. The same kind of evidence applies to the interpretation of tuberculin sensitivity in healthy persons. With the development of a simple, practicable way to distinguish persons who have had true tuberculous infections from those with other mycobacterial infections, the medical profession will be able to focus attention on the small (and diminishing) numbers infected with tubercle bacilli who are at high risk of developing tuberculous disease. Effective antimicrobial agents are now available for treatment of clinical disease. And with the present hopeful indications of effective prophylaxis, even the most conservative can look toward the day when tuberculosis will rarely be found except in the textbooks.—P. Q. Edwards and L. B. Edwards, Search for the Cause of Tuberculin Cross Reactions, *The American Review of Respiratory Diseases*, January, 1960.

CLINICAL SCIENCE

ERRORS OF MEDICAL STUDIES

George L. Saiger, M.D., New York

With an increasing number of new chemical and biological preparations on the market, the screening of some 50,000 chemicals for cancer annually, the development of new dosage recommendations for older pharmacological products, and the relentless effort to discover causes of disease, the medical profession is faced with the problem of having to rely on studies that produce results in a relatively short period of time. Unfortunately, medical research has not developed enough to operate at a fast pace and still remain reasonably accurate. Even in areas where the need for results is less pressing, sufficient research money is available to make almost any study acceptable regardless of its objectives and design. The net effect is to foster research that may direct attention to wrong avenues of approach and retard progress in a field in which it is most needed.

Thus, it has become exceedingly important that investigators exercise more care in planning and executing their studies, in analyzing the results and drawing conclusions from them, and in reporting those results and conclusions in the literature. Hill,[1] Mainland,[2] and Ross[3] have considered certain criticisms of medical studies. An attempt has been made herein to reemphasize those criticisms and also to add to them.

Sampling Bias

The researcher's ability to make an inference is not as limited as his ability to measure the degree of confidence to be placed in that inference. In order to gauge the uncertainty of an inference, he cannot exercise any prejudice or bias when he selects a sample. To select without bias is to allow every subject an equal and independent chance of being included in a sample. This is known as random sampling; the word "random" refers to the method by which the sample is chosen and not to the sample itself. Inasmuch as the composition of a random sample will vary, the sample may not be characteristic of the population which it is chosen to represent. Suppose that we are interested in a certain component of human blood and that sex is one factor that tends to make persons differ with respect to level of that component. If this were the case, we would feel quite convinced that a group at our disposal is not characteristic of the population at large if that group consisted entirely of males. On the other hand, something on the order of 50% males would give us the assurance we need. In practice, of course, there are many factors beside sex which may be relevant. Some of these factors are presumed to be known and are frequently cited. They include age, weight, and color. There are occasions when it would be difficult to say which, if any, of these factors are important and what the composition of the population is with respect to them.

Even though a random sample is not necessarily a characteristic sample, it nevertheless provides us with the only means by which to gauge the uncertainty of our inferences. Any violation of the principle of randomness results in sampling bias. Numerous examples can be cited, of which we shall mention only a few.

Stratified Sample.—A stratified sample is a biased sample unless the members of various categories are chosen at random. The categories of sex are male and female, and if there is 50% of each in the population the sample will be similarily constituted. The advantage of the stratified sample is that it does offer some assurance that the sample will be characteristic of the population and that it insures increased precision of estimate. In addition, it provides the only means by which one can obtain information about the various strata of the population as well as the population as a whole. This cannot be accomplished by random sampling alone.

Volunteer Sample.—A volunteer sample is a biased sample. The classic example can be found in studies on the effectiveness of vaccination. Children to be vaccinated frequently are admitted to a study on a voluntary basis; i. e., they are presented voluntarily by their parents. This method could influence the results of a study, and the reason is not difficult to understand.

Selection.—Vaccination can be thought of as an index of a well-informed parent's desire to safeguard his child's health. Other protective measures such as good nutrition and personal hygiene may make vaccination appear beneficial when it really is not. This type of sampling bias is known as selection. Selection need not imply that the results of a study are biased. If factors identified with selection are unimportant, the direction in which a study points may not be biased even though the sampling procedure is. It nevertheless is the responsibility of the investigator to show that such factors are unimportant.

An element of selection also may be present in studies on smoking and lung cancer, and the fact that they occasionally bear the label "prospective"

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does not make them immune to this sort of bias. For example, it is conceivable that a person's preference for smoking is determined to a large extent by his health habits in general. These habits also may govern his susceptibility to respiratory illness, and respiratory illness in turn may predispose a person to cancer. Indeed, there is evidence to suggest that pulmonary infections are rather important in the etiology of lung cancer,[4] decidedly important enough to be investigated more thoroughly.

Obviously, in order to establish a cause and effect relationship, it would be necessary to eliminate any possibility of selection. One way to eliminate selection in studies on smoking and lung cancer is to start with adolescents before they develop the smoking habit. These adolescents must be divided into two groups, either by a random process or by careful matching. One group must then be persuaded to smoke heavily and the other not at all. After these groups are studied for a considerable portion of a lifespan in a controlled environment, the incidence of lung cancer in each group can be compared. It is hard to visualize how such a study might be carried out because of ethical reasons and the difficulty of maintaining long-term cooperation. Therefore, the problem of whether or not tobacco is a cause of lung cancer must remain with us for some time, notwithstanding a recent official report to the contrary.[5] As of the moment, the best that can be said is that lung cancer may have a rather diverse etiology. Several factors have been implicated including heredity, inflammatory processes, and air pollution, of which tobacco smoke is a concentrated form. (In a sense, to accept the theory on air pollution is to accept it on tobacco as well. The evidence is circumstantial in either case.)

In consideration of criticisms raised against studies on cause and effect, it seems reasonable to conclude that the probability that a person with a certain characteristic will develop a disease is not necessarily the same as the probability that a substance identified with that characteristic will cause the disease unless it is known unequivocally that the substance is capable of producing the disease in at least one member of the species. There is an inherent contradiction to this principle in the statement that a person's risk of developing lung cancer will be reduced by the elimination of tobacco.

There is room for bias in any study in which interviewers select the persons whom they are to study. This has been the case in a recent follow-up study on the relationship of smoking to death rates for various causes.[6]

Absence or Inadequacy of Controls

A study will either establish a basis for comparison or effect a comparison itself. The use of controls is obviated when a suitable basis for comparison already exists. For instance, if a disease is invariably fatal controls as such may not be necessary in order to demonstrate the effectiveness of treatment. The same would hold true if it were widely accepted that the mortality were not 100%. Also, if the incidence of adverse effects is assumed to be nil when treatment is administered according to recommendation and if those effects will not occur for reasons other than the treatment itself, then it would not be necessary to study controls in order to prove that assumption. In general, the need for controls will depend on the strength of prevailing evidence that constitutes the basis for comparison.

When controls are included in a study, they should be comparable to the treatment group except for the factor that is being tested. If test and control groups are not comparable, any differences noted may be due to this lack of comparability rather than to the treatment itself. In order to evaluate the effects of treatment, it usually is advisable to include data on a group given a placebo. From a pharmacological standpoint, a placebo is a preparation that has all of the properties of the treatment drug except that it contains no active principle. Its effect if present is chiefly psychological. In surgical studies on animals, the analog of the placebo is the sham operation. But in such studies the primary purpose is to equalize the effects of manipulation and trauma.

It goes without saying that conditions of observation on a control group must be the same as those on a test group. In a double-blind clinical trial neither the patient nor the observer knows what treatment the patient is receiving. Consequently, it must follow that the use of a placebo is a necessary condition for a double-blind study.

The use of confidence intervals is suggested in those studies in which controls are not included. A confidence interval is a handy device for gauging the uncertainty of an inference. For example, when we determine an average value for a certain component of human blood we realize that that value is subject to sampling error. We allow for that error by defining an interval in which the true value is expected to lie. This interval is called a confidence interval.

If the researcher alternates treatment with no treatment on a random basis, as might be accomplished by the repeated toss of a coin (heads treatment, tails control) or through the use of random permutations, then he can be assured of groups of equal size as well as freedom from any selection that may bias his results. With groups of equal size, the precision of a comparison is increased. Alternatively, one can pair each person in a test group with a person in a control group by age, sex, socioeconomic status, and all other factors which seem important. Usually, this procedure is more difficult to perform than the first, but it does assure comparability of groups, provided the person who does the pairing is impartial as to the outcome of the study. Furthermore, precision is greater than in random pairing because biological variability is decreased. In fact, maximum precision is attained when a subject serves as his own control. But it is often not possible or even advisable to allow this.

Unwarranted Conclusions

We often are forced to rationalize in order to avoid the embarrassment of not being able to provide an answer to an original question that was proposed. Thus, through faulty design or analysis, we may arrive at the correct answer to the wrong problem. In statistics, such errors have been referred to as errors of the third kind.[7] (An error of the first kind is the rejection of a given hypothesis when it is true; an error of the second kind is the acceptance of that hypothesis when it is false.) Similarly, if a study intentionally is not designed to answer a specific question, then it may be hazardous to attempt to answer that question purely on the basis of evidence made available in the study itself.

Ignoring the Period of Exposure to Risk

If the period of exposure to risk is expected to vary from person to person in a study, it must be taken into account. This can be accomplished by applying the person-years concept. Each person is credited with the actual length of time in which he remains under observation while being exposed to the risk, and any comparisons are made accordingly.

Improper Interpretation of Associations

A cause and effect association or correlation cannot be established simply through the expedient of an uncontrolled association. Two variables are said to be associated or correlated if changes in one are accompanied systematically by changes in the other. A significant correlation does not necessarily indicate a causal relationship, since the correlation may be due to a common factor, particularly if time or space is involved. Thus, Professor Snedecor[8] cites an example of a high negative correlation between the birth rate in Great Britain from 1875 to 1920 and the production of pig iron in the United States. To argue cause and effect may be nonsensical. Yet the association is a statistically significant one.

Dr. Hill states the following in his book on principles of medical statistics. "Time correlations are particularly difficult to interpret but are particularly frequent in use as evidence of causal relationships—e. g., the recorded increase in the death-rate from cancer is attributed to the increase in the consumption of tinned foods. Clearly such concomitant movement might result from quite unrelated causes and the two characteristics actually have no relationship whatever with one another except in time. Merely to presume that the relationship is one of cause and effect is fatally easy; to secure satisfactory proof or disproof if it be possible at all, is often a task of very great complexity."[9]

A bit later, Dr. Hill goes on to make this statement. "It has been observed that while the death-rate from cancer has been rising the sale of bananas in England and Wales has also been increasing. No one (so far as I know) has deduced from this relationship in time a relationship of cause and effect. But such a deduction would be no less logical than many that are drawn from time relationships—e. g., the relationship of the cancer death-rate to a hundred-and-one aspects of 'modern' life."[10] These points of Dr. Hill are well taken, but they do not appear to be consistent with the thesis on which he bases his own studies on smoking and lung cancer.[11]

Statistics tend to show that in addition to an increase in the recorded death rate for lung cancer in the past several decades, there also has been an increase in the per capita consumption of cigarettes. Although we may be sensitized to the fact that this association may have no real bearing on cause and effect, what we are less apt to appreciate is that the strength of the association itself can be reduced by correcting or allowing for such factors as an aging population and an improved system of reporting, selecting, and classifying causes of death and that whatever remains could be due at least in part to improved diagnostic acumen, methods, and facilities and to an increased awareness of cancer on the part of the medical profession and the public.

Miscellaneous Errors

Quantity Versus Quality in Experimental Medicine.—Even if several independent studies indicate the same conclusion, this conclusion will not necessarily be correct if the same fundamental fallacy is present in each. Also, a large number of samples will not compensate for faulty design and poor experimental technique. Many authors have a tendency to publish the same material in several journals, thus overemphasizing or perhaps exaggerating the importance of their findings. Such practices often border on sensationalism and should be discouraged. Quantity is never a substitute for quality in experimental medicine.

Error of Extrapolation.—Extrapolation from animal data to human experience nearly always is hazardous. The fact that a successful cancer treatment in animals rarely proves successful for man may lend credence to this statement. Extrapolation is just as dangerous in studying cranberries and lipstick as in anything else.

Failure to Appraise the Appraiser.—Before accepting someone else's appraisal of a study, one must be sure that he also does not have a proverbial axe to grind. Otherwise, he may bias the appraisal in his favor. An appraisal is best made by a person who not only is an expert in a field but who also is reasonably disinterested in the particular direction in which a study points.

Failure to Investigate or Report Adverse Effects.—The dangers of treatment are no less important than the assumed beneficial effects. Animal studies on toxicity are of definite value. But they do not replace the need for assessing the nature and extent of adverse effects in humans. So-called side-effects may be severe enough to render an otherwise useful preparation useless. Unfortunately, this has been the fate of many chemicals that seemed to hold promise in cancer therapy.

Failure to Recognize an Ethical Problem.—Nearly every clinical trial involves some ethical problem. Failure to recognize this problem or to devise means to cope with it is the most serious error that can be committed in a medical study. A typical example concerns the advisability of withholding treatment when it may possibly be of value. Of course, the problem is more easily stated than solved. The object is to retain the best design under the conditions permitted, and the conditions permitted are those dictated by the experience of others[12] and the conscience of the investigator.

Comment

It seems appropriate to end this discussion with the following quotation. "The facts of medicine are (1) that there are few if any facts in it and (2) that what passes for facts—that is, interpretation of currently available data—must be re-examined frequently."[13]

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POSSIBILITIES OF INDIVIDUAL RESEARCH IN ANTIBIOTICS.—In the search for new antibiotics the empirical method of screening unknown substances has been extremely successful in the past, as witness the major extensions in antibiotic therapy achieved. As well, there are indications that a rational approach to new antibiotics will be more extensively pursued in the future, probably along the lines of partial synthesis such as with the penicillin nucleus or by total synthesis of polypeptides, as has already been shown for gramicidin S and some of its analogues (Schwyzer & Sieber, 1956). That there are other possibilities is evident from the recent development of griseofulvin from a laboratory curiosity to the first systemic agent effective against dermatophytes. . . . Its importance in the present context is that griseofulvin's status owes nothing to the screening of unknown substances. In fact the fungistatic action is of such an extraordinary kind that the selection of griseofulvin as an antifungal antibiotic would have been most unlikely from its demonstrable activity on an assay plate. Instead, the conventional screens uncovered numerous members of the polyene group of antifungal substances, none of which have proved of value against the common fungal diseases caused by the dermatophytes. . . . For the development of griseofulvin, the clues lay in the nature of the disease process, the exceedingly low mammalian toxicity together with the affinity of the antibiotic for keratinous cells, and the fungistatic action evident on the growing tips of the hyphae. Thus, to extend the present range of antibiotic therapy, it may well not be enough to rely on the mechanics of a screen. There is a need for a biological curiosity about the nature of the antibiotic action disclosed, as well as a full understanding of the whole disease process. Might it not be that this could restore to the individual worker the power to make an antibiotic discovery fit to rank with Fleming's penicillin?—A. H. Campbell, B.Sc., Ph.D., The Search for New Antibiotics, *British Medical Bulletin*, Jan. 1, 1960.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION

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DOCTORS' COMMONS

THE American Medical Association will celebrate the 112th year of its founding next week in Miami Beach. This Association is only 16 years younger than the British Medical Association, which began as a small and provincial society in 1832. Paul Vaughan[1] has prepared a short history of the British Association which was printed a few months ago in Guildford and London. The annual scientific meetings of the B. M. A. had spun off the affairs devoted to business and medical politics by 1865 and had concentrated upon communications of clinical and research interest. Lord Lister, a frequent speaker in the Section of Surgery, gave one of his first descriptions of the action of his new carbolic spray in 1871. The *Lancet*, under the spell of Wakley, regarded Lister's address as nothing new, and "disbelievers in the marvelous efficacy of carbolic acid could not fail to notice that with every public appearance Professor Lister's solutions become weaker and weaker, while his faith appears to grow more and more."

Medicine, surgery, and obstetrics were the three branches of medical training that held specialty sessions a century ago in England. The number of sessions increased as medical science became more complex. There were 19 sections at the Annual Meeting in 1957. This compares with 22 sections for our meeting in June in Miami Beach. Plenary sessions and round-table conferences (panels) were not introduced until 1945. Annual Clinical Meetings were begun in 1958, for reasons similar to the institution of the Clinical Meeting in the United States, i. e., the need for greater geographic distribution of annual meetings and the need for emphasizing clinical contributions.

The true ancestor of the *British Medical Journal* was the *Midland Medical and Surgical Reporter and Topographical and Statistical Journal*. The *Reporter* ceased publication in 1833. The function was taken over by the *Provincial Medical and Surgical Journal* which became the *British Medical Journal* in 1857. One policy expressed by the editors in 1840 has been maintained, "We make it a rule to interfere as little as possible with an author's expression of his sentiments or ideas."

The reputation of the *British Medical Journal* spread in the following years, even to America, where some of its virtues were readily recognized. Doctor J. C. Warren of Boston, familiar with the advantages of the British Journal, urged the establishment of a similar publication in America and suggested that at its head, we select "an editor with a vigor equal to that of Mr. Hart (editor of the *B. M. J.*) that he might, with his editorial staff, stir all the dry and mouldering members into a new life, and that he might infuse into them an interest and activity equal to or even greater than that which the British Association shows today." Hart's philosophy also included "Better papers, more condensation, and a larger wastebasket." But all was not on the plus side. There was a considerable body of sentiment in support of the premise that each editorial should be signed and that the advertising committee be made public. The Council replied that any principle other than anonymity was impractical and that its advertisements were subjected to careful scrutiny. In order to implement the policy, an Editorial Committee was thereupon appointed (1889) which would review and approve at a meeting scheduled each Thursday the proof of each page of advertising.

Another clash between the editor and Lord Lister, according to Vaughan, "immensely strengthened the position of the *British Medical Journal*, but it also provided a critical test for the Association itself." Nevertheless, the B. M. A. rejected Lister's criticisms and supported the policies of the editor.

Dawson Williams, a career man, became the full-time editor of the Journal, the first in the Association's history, in 1902. The chief function of the Association, according to Williams, was the advancement of medical science and the honor and interests of the medical profession. He conceived of the Journal as the indispensable tool in postgraduate training. He gained "a freedom of comment which was considered essential if the *Journal* was to preserve a proper independence within the Association. The Editor's comments were not always in tune with official policy, and sometimes stimulated wrathful protest from influential members of the Association." More and more articles which appeared in the Journal were discussed in the popular press and were widely publicized. The subject frequently was discussed originally in the *British Medical Journal*, commented on in the London *Times*, and later became the subject of editorial comment "up and down the press of the country."

One-half of the cover page was given to advertisements prior to 1937. On that year a typographer of great distinction was given the assignment of designing a new cover page for the Journal, having received acclaim for his redesign of the format of the London *Times*. When he was first shown a copy of the Journal he stated, "It looks more like a boiler-maker's magazine than a doctors'." The old-fashioned type, the cumbersome printers' rules of boxing off each column, the Gothic title—everything was changed. The reform went still further. The old composing machinery was removed from the Association offices and the Journal was printed elsewhere, thereafter. The familiar, new gray-blue cover, without advertisements, has been maintained. These changes are strangely reminiscent of the J. A. M. A. Progress has been made in modifying the cover of the J. A. M. A. Revision of the editorial contents will be a slower and more laborious procedure for us.

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[1] Vaughan, P.: Doctors' Commons, London, Heinemann, 1959.

MAY DAY-EPILOGUE

Reference to the annual parleys of the Old Turks, the Young Turks, and the Young-Young Turks in Atlantic City early in May of each year has been made in two editorials in The Journal (171:2102, 1959 and 172:1772, 1960) in recent months. Two other conferences deserving of editorial comment were firmly launched in conjunction with these assemblies. The Chief Editors of each of the Specialty Journals (ten in number) of the A.M.A. held an all-day conference on May 1 to exchange ideas and to offer suggestions in each of their respective areas of specific interest that might contribute to the betterment of the periodicals in other fields. Three of the Chief Editors of the Specialty Journals were in their first year of assignment. Dr. Warren E. Wheeler, Professor of Pediatrics, University of Ohio, was designated Chief Editor of the *A.M.A. Journal of Diseases of Children* late last year as a successor to Dr. Richard Day, who asked to be relieved of his duties prior to acceptance of the professorship of Pediatrics at Pittsburgh University. Dr. George E. Shambaugh, Professor of Otolaryngology at Northwestern University, was appointed Chief Editor of the *Archives of Otolaryngology* early this year. He replaced Dr. George M. Coates, who died literally in the harness at the age of 82 years. He had served with the *Archives of Otolaryngology* for 22 years. Dr. David C. Cogan, Professor of Ophthalmology, Harvard Medical School, and Director of the Howe Laboratory of Ophthalmological Research of the Massachusetts Eye and Ear Infirmary, was the third draft. Doctor Cogan replaced Dr. Francis H. Adler, who had served for 32 years on the *Archives of Ophthalmology*, first as a member of the Editorial Board and for the past 11 years as Chief Editor of that Journal.

One decision of importance to many physicians was the announcement at this conference of the approval by the Board of Trustees of the American Medical Association of the deletion of the letters "A.M.A." from the title of each of the Specialty Journals. This policy will become effective July 1, 1960. Some librarians may be unhappy with this decision, but it is believed to be a desirable one for most interested parties. With the deletion of "A.M.A". from the title, the pediatric journal will revert to its original title, *American Journal of Diseases of Children*. Another Specialty Journal has undergone a major title revision. The *A.M.A. Archives of Industrial Health*, as of July 1, 1960, will become the *Archives of Environmental Health*, with specific emphasis on Preventive Medicine, Industrial Health, and Aerospace Medicine. A joint conference of the Chief Editors of the Specialty Journals and members of the Scientific Committee of the Board of Trustees of the A.M.A. will be scheduled annually.

The Association of Professors of Medicine met on the preceding day in the same city. This organization is composed of the Head of the Department of Medicine in each medical school in the United States. This Association was established during the last year under the leadership of Dr. Robert H. Williams, Professor of Medicine at the University of Washington. It evolved from annual meetings held by smaller groups during the last six years. One of the major objectives of this Association is the formulation and execution of policies that are most desired for optimal accomplishments in academic medicine and in the practice of medicine; the Association has collaborated extensively with other medical groups in attaining these goals. The very enthusiastic participation this year of its members helps assure future progress. The A.M.A. was represented at the meeting by staff members from the Council on Medical Education and Hospitals.

Subjects of mutual interest were discussed at special and plenary sessions. Although one might assume that the members of the Association share opinions in common because they share problems in common, such an assumption proved to be false. A wide divergence of sentiment was expressed on each of the subjects, but particularly on the delineation of the responsibilities of the Head of the Department of Medicine. How much time should be allocated to teaching, research, public relations, national activities, and consulting practice? What responsibilities should be delegated to other members of the department? Should a Business Manager serve in those departments that comprise a large staff and pursue an equally large research program? What is the best course of conduct for teaching students, interns, residents, research fellows, and postgraduate students? What is the best means of furthering the intellectual goals of the individual heads of the departments themselves? It is clear from this query that they accept the premise that their education is not finished with the assumption of the headship of the most important clinical department in the medical school. How best can private patients be used in the teaching program? How can total patient care best be rendered? Since the cost of hospitalization is skyrocketing, can the outpatient be utilized to a greater extent for teaching as well as patient care and be an effective substitute for inpatient care?

The Chief Editors of the Specialty Journals of the A.M.A. and the Association of Professors of Medicine have vital missions to perform in American medicine. It is manifest that the achievements of each group will be commensurate with the intellectual capacity of the persons who have assumed their respective responsibilities.

HYDRALAZINE SYNDROME, AN "EXPERIMENT OF NATURE"

A decade ago, when hydralazine was used first in the treatment of hypertension, a significant number of patients developed a peculiar reaction that was later identified as the "hydralazine syndrome." The initial symptoms closely mimicked rheumatoid arthritis. The fully developed reaction mimicked the clinical picture of systemic lupus erythematosus (SLE), except for one or possibly two notable differences.

The difference that is most apparent is the absence of renal involvement in the hydralazine syndrome in man. This lack of renal disease is, however, based purely on negative urine findings, in contrast to the positive findings at one stage or another in more than 60% of patients with SLE. There is not enough evidence to rule out the occurrence of renal involvement with finality in this reaction to hydralazine. Renal lesions have been produced by administration of hydralazine in dogs. Also, renal biopsies have revealed that histological changes of SLE may precede any abnormalities in the urine. Finally, timing may be misleading in studies in man, since the drug is withdrawn as soon as a hydralazine syndrome is diagnosed. Renal involvement might have appeared if the drug had been continued. There are no studies of renal biopsies in this type of drug reaction in man.

A second possible difference between spontaneous SLE and the hydralazine syndrome concerns the persistence of the latter. It has been assumed in the past that the hydralazine syndrome would disappear after the drug was withdrawn. Recent evidence indicates that this may not be the case, as is presented in this issue of THE JOURNAL, p. 657. In all instances in which this syndrome persisted, however, the course was typically benign and not cyclic. Although SLE can be similarily benign, usually it is not. One wonders what the results would be if a larger series of patients were followed for comparable periods of time, or if the drug were not stopped promptly after diagnosis of the reaction. One is forced to suspect that it may be of greater importance than its occasional clinical occurrence would indicate.

Several mechanisms of the origin of the reaction have been postulated. A theoretical suggestion, for which there is no proof, is that SLE represents a hypersensitivity to several agents, one of which is hydralazine. Another explanation is the activation of latent SLE on hydralazine. However, it would seem strange indeed if 10% of all hypertensive patients selected for hydralazine therapy were instances of latent SLE. Most investigators assume that the hydralazine syndrome is a drug reaction of uncertain etiology—possibly hypersensitivity, possibly a toxic state, or even a chemically induced deficiency of a trace metal or some other essential substance. Genetic predisposition because of a metabolic peculiarity could be a factor, similar to that observed in certain racial groups in which drug-induced anemia is due to inadequate activity of glucose-6-phosphate dehydrogenase.

Hydralazine is endowed with a strong affinity for metallic ions. Comens[1] has proposed that this chelating action may produce a trace metal deficiency leading to interference with certain enzyme systems. Experimental evidence has led him to believe that possibly manganese is the metal depleted. Besides the chelating action, it has been reported that hydralazine can combine with carbonyl and sulfhydryl groups, can inhibit histaminase, and can compete with glucosamine as a substrate for acetylation. Whether any of these metabolic effects is related to the hydralazine syndrome or SLE has yet to be proved.

The suggestion arises from our present information that the study of the immunological and metabolic aspects of the unique hydralazine reaction may illuminate some of the obscure aspects of SLE and rheumatoid arthritis. Certainly, the available means for studying the questions raised by this peculiar clinical entity have increased greatly since the syndrome was first described in 1953. Despite the development of new means of investigating the problem, few have been utilized. Today, any new instance of this syndrome that may arise should be looked upon as a rare opportunity for the clinical investigation of this important problem.

CALCIFICATION IN DIABETES

Soft tissue calcification is a subject of broad and fundamental interest. It has been treated generally from the point of view of supposed etiology, mainly as to whether this represents a general systemic disease in which calcium deposition occurs because of increased serum calcium content (metastatic) or whether it represents a change in local tissue reactions (dystrophic or degenerative). Localized calcification from changes in tissue response is related to infection; local vascular change, as in chronic venous insufficiency; trauma; and tissue degeneration of aging. In some diffuse systemic diseases there may be extensive soft tissue calcifications which are purely dystrophic in type, notably subcutis calcification or ossification, or both, in dermatomyositis and scleroderma and arterial wall calcification in atherosclerosis.

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[1] Comens, P.: Chronic Intoxication from Hydralazine Resembling Disseminated Lupus Erythematosus and Its Apparent Reversal by Manganese, in Metal-Binding in Medicine, edited by M. Seven and L. A. Johnson, Philadelphia, J. B. Lippincott Company, 1960, pp. 312-320.

[1] Lippman, H. I.: Subcutaneous Ossification in Chronic Venous Insufficiency, Angiology 8:378-396 (Oct.) 1957.

It is universally believed that degenerative tissue disease of aging occurs earlier and is more extensive in patients with diabetes. The occurrence of arterial calcification in a patient with diabetes would naturally follow the degenerative process in vessel walls. With the increased use of radiologic examination, it has been noted that wall calcification occurs in the vas deferens. As cases have been collected and reported it has become evident that vasal calcification is more prevalent in patients with diabetes. It is probable that this somewhat parallels the degree of degenerative disease of the vas deferens.

In this issue of The Journal there is a statistical communication in which this problem is surveyed and some interesting conclusions are presented. The lack of correlation between vas deferens calcification and vascular calcification is somewhat surprising but valid statistically. It may be that there is some hormonal factor which influences this, as has been suggested in subcutis ossification of the lower extremity in patients with chronic venous insufficiency.[7]

MEDICAL RESEARCH

Perhaps the time has come to review at least one phase of medical research, the investigative phase. The perplexing problem today is not that the causes of arteriosclerosis and lung cancer evade us but that we evade the causes. First of all, what are our attitudes toward medical research in general, and how much faith can we place in it? What has medical research meant to those concerned, the investigator, the practitioner and the public?

In some instances, it has provided a means whereby one can establish himself in the scientific community irrespective of the quality of his output. It has created an environment favorable to expounding theories which may be based on little more than fantasy. It has meant that some research can be motivated by expediency—the zeal to produce for the sake of recognition, the pressure to accede to the demands of a service, and the urge to present a paper at a scientific meeting in order to qualify for an expense-free holiday.

It often has been characterized by an inability to cope with scientific problems at a level ordinarily expected of industry and agriculture. On occasion, it has permitted the expert to act on a hunch before submitting that hunch to scientific scrutiny. It has placed the clinician in the role of the statistician and the statistician in the role of the clinician. It has meant a frequent unwillingness on the part of the investigator to abandon theories which govern the transmission of infectious diseases when confronted with problems relating to mental disorders, hypertension, and automobile accidents.

It has compelled the practitioner to function in the capacity of an expert and understandably so. He is the one who must disentangle a maze of conflicting opinion before he can practice his art. What about the public? At one moment, they are advised to restrict the saturated fatty acids in their diet and at the next moment provided with information that would cast doubt on the value of such a regimen.

It has forced the medical profession to ask itself: Do our experts possess sufficient candor and altruism? Must they choose sides in order to resolve an issue? Is there no middle-of-the-road policy? Must some medical problems be treated as political issues, or are there ways to sit down at a conference table in an atmosphere of peaceful coexistence, weighing the evidence for and against and arriving at the type of solution that will benefit mankind? Is this where we have failed with regard to anticoagulants, water fluoridation, and radiation genetics, as well as arteriosclerosis and lung cancer?

Has the average critic been willing in his appraisal to allow for the limitations of medical research, to conceive of the notion that a disease does not necessarily have a single cause, that in many instances the type of research necessary to establish a cause is virtually impossible to conduct among human populations, that there is as yet no clear medical definition of a cause, and that far-reaching results are not achieved overnight? This subject is presented clearly in a communication in clinical science, this issue, page 678.

Where must we begin? Is it not the primary responsibility of every investigator to familiarize himself with the various errors that may affect his own experiments? By recognizing these errors, he may take steps to avoid them; by avoiding them, he may attain a level of performance that will ultimately lead to the discovery of what causes cancer and what predisposes to sclerotic degeneration of the arteries. For it is this performance, modest as it may be, that will set the standards and provide the impetus for future investigation. It is this performance that will regain the faith of the practitioner and the public and turn the wheel of science forward.

THE NURSE AND THE DOCTOR

At the turn of the century, for every physician in practice there was one other professional health practitioner. Today the ratio is one physician to four[1]; two of these four are nurses. Fifty years ago there were 149 physicians and 89 nurses for every 100,000 persons in the United States. Today for 100,000 population there are 133 physicians and 268 professional nurses, aided by an almost equal number of nursing auxiliaries of various kinds.[2] Such statistics—indicating as they do nursing's rapidly growing share of responsibility for modern health care—underscore the importance of certain actions taken in Atlantic City, June, 1959. The A. M. A. House of Delegates, through adoption of a report and resolutions, noted "a reactivated intent to establish an effective liaison with our nursing colleagues based on the best possible mutual understanding and respect."

That reactivation, implemented by the Board of Trustees' Committee for Liaison with National Nursing Organizations, "must be supplemented by similar interest and concern on the part of component and constituent societies, and indeed on the part of each individual physician." The report also stated that the specific steps recommended include initiating "physician participation at the grass roots level in all new or proposed nurse education programs" and effecting "enlightened physician representation on advisory boards to nurse educational authorities and on nurse licensing organizations at the state level." Such community relationships are highly desirable. Yet a physician who is to approach them wisely may profit by review of several items. No editorial can reveal in a few paragraphs the comprehensive data that the physician liaison-seeker will need. The following information is pertinent, however:

1. The nation's supply of active registered nurses is now ninefold that of half a century ago. This has exceeded the supply of physicians.

2. The extension in kinds and quality of services required of nurses has been more dramatic than the growth in quantity demands. The march of medicine, the expansion of hospitals and health agencies, the army of nursing auxiliaries to be taught and supervised, and; last but far from least, the delegation by doctors to nurses of many of the tasks they themselves once performed, are creating many new and demanding roles for nurses. As a result, different "levels" of nurses are emerging, with varied abilities and preparation. The leaders in the nursing profession maintain with justice that physicians and hospital administrators, in the interests of patient safety, must learn to distinguish more clearly between these skill levels, perhaps even before all nurses understand and concur in the differentiations.

3. Rapidly advancing quality as well as quantity demands on nurses are forcing a transition in nursing education that is comparable in magnitude to the changes in medical education that followed publication of the Flexner report in 1910.

4. The variety of nursing education programs in existence, which physicians find confusing, may to a certain extent be transitional but grow largely out of the necessity to prepare some nurses for emerging new responsibilities and increase over-all service supplies.

5. The aggressive motive for much of nursing is in the little understood and often maligned graduate education programs that lead to a Master's and a higher degree. Such programs prepare the teachers, administrators, supervisors, and nursing specialists who, in turn, determine both quantity and quality of all nursing services delivered at the bedside and elsewhere. The greatest proportional shortage exists in this group. The National League for Nursing estimates that 13% of the 460,000 active nurses in the country are in positions for which they should have preparation now offered only in graduate study, yet less than 2% have qualified for a Master's degree. The greatest numerical total of position vacancies is in the bedside nursing ranks. The filling of these bedside positions depends on the development of more good teachers and other leaders.

6. Three kinds of schools offer both classroom work and hospital bedside experience in preparing students to take state examinations for R.N. licensure and beginning nurse positions. First, graduates of the four-year collegiate professional programs give direct patient care in hospitals and public health agencies but are usually able to assume more independent responsibility than are the graduates of shorter training programs and are eligible, if they wish, to pursue graduate study. Second, the three-calendar-year hospital diploma schools continue to graduate more than 80% of all registered nurses. Third is a new type, the two-academic-year associate degree technical program now offered by more than 40 community or junior colleges throughout the country. It is designed not to supplant the older programs but as an additional, different, and speedier means to meeting society's need for bedside nurses.

7. One-year vocational and hospital schools prepare practical nurses for less complex nursing duties or for full care of the chronically ill or the convalescent.

8. A great amount of short on-the-job training is being given to various types of nursing auxiliary workers. Also many refresher or retraining courses are held. Such in-service education accounts in part for the sharply increased need for nurses with advanced preparation.

9. Physicians who are anxious to promote the evolution of nursing education will need to know that nurses are questioning whether they should go on indefinitely accepting responsibility for giving more and more of the medical treatments that physicians—admittedly hard-pressed—are seeking to assign to them. Often the pressure to perform medical tasks has forced nurses to turn over to inadequately prepared auxiliaries the ministrations that are the heart of nursing care. This may lead to the dissatisfaction of doctors as well as patients and nurses. Democratic interdisciplinary consideration of this one area alone might, in many hospitals, yield rich returns in immediately improved patient care as well as guides to future educational efforts.

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1. Physicians for a Growing America, report of the Surgeon General's Consultant Group on Medical Education, Public Health Service Publication no. 709, 1959, p. 65.

2. (*a*) Reference 1, p. 2. (*b*) Facts About Nursing, 1959, American Nurses' Association, pp. 7 and 14. (*c*) Building America's Health, report of the President's Commission on Health Needs of the Nation, pp. 115 and 164.

MEDICAL NEWS

ALABAMA

Dr. Pigman Goes to New York City.—Ward Pigman, Ph.D., was appointed professor and chairman of the department of biochemistry at New York Medical College. Dr. Pigman, associate professor of biochemistry at the Medical College of the University of Alabama, Birmingham, will assume his new post at the end of this academic year. He will replace Israel Kleiner, Ph.D., who is retiring after serving New York Medical College for many years. Dr. Pigman is a consultant for the National Institute of Health, United States Navy, and the National Research Council. He is the recipient of the C. S. Hudson Award of the American Chemical Society.

CALIFORNIA

Course on Medicine in Law.—On June 25-26 the University of California School of Medicine will present "Medicine for Lawyers." The course is designed to bring to attorneys some of the aspects of medicine, surgery, and psychiatry with which they are brought into day to day contact in their own practices. Stress will be on the relevant medical problems and techniques, and adequate time for discussion will be available at the end of each session. Registration is limited. Session topics include orthopedic problems, psychiatry, and the changing field of medicine. For information, write the University of California School of Medicine, Department of Technical Education, San Francisco.

COLORADO

Dr. Wasson Receives Alumni Award.—Dr. W. Walter Wasson, Denver radiologist received the Norlin Award, highest decoration given by the Associated Alumni of the University of Colorado, at the June 2 university commencement exercises in Boulder. The Norlin Award was named for the late President George Norlin of the University of Colorado and is given annually to a person or persons who attended the university and later attained "great distinction" in their field of endeavor. Dr. Wasson earned his bachelor's degree from the university in 1908 and was graduated as a doctor of medicine from the University of Colorado School of Medicine in 1910. He is a past-president of the Radiological Society of North America, co-founder and chancellor and vice-president of the American College of Radiology, vice-president of the American Roentgen Ray Society, and for several years was chairman of the scientific exhibit awards committee of the American Medical Association.

CONNECTICUT

University News.—Thomas R. Forbes, Ph.D., associate professor of anatomy, and Dr. Arthur Ebbert Jr., associate professor of medicine, both assistant deans, have been named associate deans of the Yale University School of Medicine as of July. Dr. Forbes supervises student affairs, and Dr. Ebbert is in charge of postgraduate medical education. ——A gift of $110,000 has been made to Yale University for the Cardiac Fund of the Yale–New Haven Medical Center by the Victoria Foundation, Inc. The contribution will be used to construct a new surgical suite, including a cardiac operating room and an adjoining control room for necessary electronic equipment. According to medical center authorities, the new quarters will eventually become part of an entirely new 10-room operating pavilion to be built in the next year. The new operating suite will replace an area of the existing Farnam Operating Unit which was constructed in 1930.

DISTRICT OF COLUMBIA

Dr. Copeland Goes to Texas.—Dr. Murray M. Copeland resigned as professor of oncology at Georgetown University Medical School to go to the University of Texas M. D. Anderson Hospital and Tumor Institute of the Texas Medical Center at Houston on July 1. He will become assistant director for education. Dr. R. Lee Clark, director of the M. D. Anderson Hospital facility, in announcing the appointment indicated that, while Dr. Copeland's primary function will be with the office of education, his duties will include professional and public relations, with coverage of the office of director in Dr. Clark's absence. Dr. Copeland has been associated with the Georgetown University Medical Center since 1947 as head of the oncology department.

FLORIDA

Society News.—The Florida Radiological Society held its annual meeting April 10 at Jacksonville. The new officers for this year are: Drs. John S. Stewart, Fort Myers, president; John P. Ferrell, St. Petersburg, president-elect; Ivan Isaacs, Jacksonville, vice-president; Richard D. Shapiro, Miami Beach, treasurer; Alfred G. Levin, 837 DuPont Building, Miami, secretary; and councilor to American College of Radiology, J. Maxey Dell Jr., Gainesville.——Officers by the Greater Miami

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Radiological Society elected Jan. 20 are: president, Dr. Andre S. Capi, Hollywood, vice-president; Dr. George P. Daurelle Jr., Miami; secretary-treasurer, Dr. Donald H. Altman, 2751 Coral Way, Miami. Meetings are held on the third Wednesday of each month at 8 p. m. at Jackson Memorial Hospital.

GEORGIA

State Medical Election.—The new officers of the Medical Association of Georgia are as follows: president, Dr. Milford B. Hatcher, Macon; first vice-president, Dr. Simone Brocato, Columbus; second vice-president, Dr. Braswell E. Collins, Macon; secretary, Dr. John T. Mauldin, 340 Boulevard, Atlanta; president-elect, Dr. Fred H. Simonton, Chickamauga; immediate past-president, Dr. Luther H. Wolff, Columbus; speaker of the house, Dr. Thomas W. Goodwin, Augusta; and vice-speaker, Dr. J. Franklin Walker, Atlanta.

ILLINOIS

Society News.—On April 20 the following members of the Illinois Psychiatry Society were elected to office for the year 1960-1961: president, Dr. Joel S. Handler; president-elect, Dr. Melvin Sabshin; secretary-treasurer, Dr. Harold M. Visotsky; councilors, Dr. Frances Hannett and Dr. Jackson A. Smith; delegate to the American Psychiatric Association assembly, Dr. Paul E. Nielson; alternate delegate, Dr. Jewett Goldsmith. All are from Chicago.

Chicago

Hospital Staff Alumni Meeting.—The Swedish Covenant Hospital House Staff Alumni Association will hold its inceptional meeting June 20, 6:30 p. m. This will be a dinner meeting in the hospital, 5145 N. California Ave. The organization will include former interns and residents, and externs of one or more years service. Efforts are presently being made to contact eligible members. Anyone interested in membership is urged to write the Office of the Administrator.

Annual Dustfall.—The Armour Research Foundation reported that Chicago's dustfall for 1959 was the lowest in the past 11 years. The past year also was the third straight year that the dustfall average had diminished. An average of 48.8 tons per square mile fell each month last year, 13.5% less than the previous 10-year average of 56.4 tons per square mile per month. The foundation, an affiliate of Illinois Institute of Technology, revealed the following annual average total dustfall readings (tons per square mile per month) for Chicago over the past 10 years: 1949 (58.3), 1950 (59.0), 1951 (63.4), 1952 (56.2), 1953 (53.6), 1954 (56.6), 1955 (53.4), 1956 (57.1), 1957 (54.4), and 1958 (52.1).

Study of Factors in Death Rate.—The University of Chicago was awarded a $1,017,000 grant to conduct a study on the 500,000 Americans who will die between May 1 and Aug. 31, 1960. The grant, from the Public Health Service, National Institutes of Health, U. S. Department of Health, Education and Welfare, will enable university researchers to undertake the "most thorough study ever attempted to pinpoint differences in the death rate." By disclosing the role of various personal, social, and economic factors on the causes of death, the project "will furnish a picture of where the battlefront lies and what the next steps should be to cut back deaths," said Philip M. Hauser, chairman of the department of sociology. The study will be based on a matching of death records for 1960, collected by the National Office of Vital Statistics, with population and housing schedules collected by the Bureau of the Census in the April census. The project will be completed sometime late in 1965. Facts on all persons dying in the months of May, June, July, and August, 1960, will be taken from the April census schedules. The information reported will be used to classify deaths by various social and economic characteristics of decedents, as well as place of residence. The most important characteristics for which mortality differentials will be analyzed are geography, ethnicity, income, occupation, education.

MAINE

Annual Session in Rockland.—The 107th annual session of the Maine Medical Association will be held June 19-21 at the Samoset, Rockland. The program includes the following topics and speakers:

Cancer, Dr. Danely P. Slaughter, Chicago.
Carcinoma of the Prostate, Dr. Perry B. Hudson, New York City.
Space Medicine is Coming Down to Earth, Dr. Hugh C. MacGuire, Montgomery, Ala.
Progressive Hospital Care, Edward J. Thoms.
Surgical Aspects of Cerebral Vascular Accident, Dr. James L. Poppen, Boston.

Specialty group meetings are planned on surgery, hypnosis, the eye, anesthesiology, obstetrics and gynecology, pediatrics, internal medicine, radiology, general practice, and medical legal involvements. For information, write Dr. Daniel F. Hanley, P. O. Box 240, Brunswick, Maine, Secretary.

MASSACHUSETTS

Three Students Receive "Good Physician" Awards.—Mark Hedge Cooley, of Kingston, Morris Dratch, of Mattapan, and Jordan J. Cohen, of Brookline, fourth-year medical students at Boston University, Tufts, and Harvard, respectively, were named winners of the Massachusetts Medical Society's "good physician" award. The students were presented with their awards at the annual dinner of the society's council May 16. The awards are given appreciation of "diligent work in the medical school by one who best exemplifies those intangible qualities which serve to designate him as a good physician." Mr. Cooley has held the number one position in his class for the past three and one-half years. He has been president of the first-year class, treasurer of the Student Council, and is currently president of the local chapter of Alpha Omega Alpha. Mr. Dratch ranks fourth on the basis of three years' work. He received the Medical Class of 1928 Award for outstanding work in anatomy his first year, and has held a student research fellowship in biochemistry. Mr. Cohen received his A.B. from Yale, magna cum laude, in 1956.

MICHIGAN

Hospital Alumni Meeting.—The annual reunion of the Sinai Hospital of Detroit Alumni Association will be held June 22. The program will include scientific presentations by the house staff, a lecture by Dr. Rachmiel Levine, Chicago, guest lecturer, and lunch at Sinai Hospital. In the early afternoon a department of medicine clinical conference will be held with Dr. Levine as guest participant. In the evening a banquet preceded by a cocktail party at 6:30 p. m. will be held at Franklin Hills Country Club. For information, write Sinai Hospital of Detroit, 6767 W. Outer Dr., Detroit 35, Attention: Director's Office.

Meeting on Chronic Disease Control.—A two-week Institute on Chronic Disease Control will be conducted June 13-24 at the University of Michigan School of Public Health, Ann Arbor. Public health physicians and nurses, nutritionists, and health educators attending the institute will meet to (1) review the current status of chronic disease public health programming; (2) exchange information and ideas; (3) consider new approaches to chronic disease control; (4) develop a publication on chronic disease public health programming. Dr. Valdo A. Getting, professor of public health practice, is chairman of the planning committee. The program is co-sponsored by the Michigan Department of Health, U. S. Public Health Service, Association of State and Territorial Chronic Disease Program Directors, and supervisors of chronic disease teaching programs in schools of public health. Registration fee is $50 for the two-week session.

New Medical Program at Wayne State.—A new program in medical education at Wayne State University called the 2-4-2 plan was explained May 18 to liberal arts advisors from 20 Michigan universities and colleges by Dr. Morton Levitt, assistant dean of the College of Medicine, who said the new plan will provide students with a "broader liberal arts background as well as a more effective medical education." The program will provide the opportunity for earlier professional selection and enable the student to elect both the Ph.D. and M.D. degree "without the usual loss of time." After September, 1961, almost all students will be admitted to WSU College of Medicine either through the 2-4-2 plan or with a bachelor's degree. The 2-4-2 program, which Wayne educators have spent five years planning and executing, involves two years in the College of Liberal Arts for completion of both liberal arts and premedical requirements. The next four years will be divided between the College of Liberal Arts and the College of Medicine. During this period, the medical student will have an integrated program of study leading to the bachelor's degree and completion of the basic medical sciences. The final two years will be spent in clinical training at the College of Medicine and its affiliated hospitals.

MINNESOTA

Graduate Session on Health Statistics.—The University of Minnesota College of Medical Sciences School of Public Health is the host institution for the third cooperative summer program in statistics in the health sciences to be presented by the accredited Schools of Public Health of the United States during the summer of 1960. This program is made possible by a research training grant from the Division of General Medical Sciences, National Institutes of Health. The summer program is for statisticians, epidemiologists, public health personnel, professional workers, graduate students, research workers, teachers, and other interested persons. The program is designed to meet educational and training needs of those engaged in work in health and health-related agencies. Courses to be offered will consider statistical methods in public health, management of health agency records, biostatistics in the health sciences, and demographic methods in public health. Stipends are available for attendance. For information, write the University of Minnesota, Department of Biostatistics, 1226 Mayo, Minneapolis 14.

PENNSYLVANIA

Two Physicians Cited for Services.—Dr. Kenneth M. Day, of Pittsburgh, an otologist who has been nearly deaf for many years, received a distinguished service award May 20 from the Pennsylvania and New Jersey Academies of Ophthalmology and Otolaryngology at a joint annual meeting attended by eye, ear, nose, and throat physicians from six Middle Atlantic states, "in honor of his service to medicine and mankind." A similar distinguished service citation was awarded to Dr. James S. Shipman, of Moorestown, N. J., an ophthalmologist and educator associated with Philadelphia's Wills Eye Hospital and the University of Pennsylvania. Dr. Day is reported to be the first physician in the United States to limit his practice to otology. Dr. Shipman is a founder and former president of the New Jersey Academy of Ophthalmology and Otolaryngology.

Philadelphia

Dr. Ersner Honored.—The Temple University Medical Center honored Dr. Matthew S. Ersner, emeritus professor of otorhinology, at a portrait presentation April 20, in the School of Medicine auditorium. Dr. William N. Parkinson, vice-president of Temple University in charge of medical affairs, accepted the portrait in behalf of the school from Dr. David Myers, head of the department of otorhinology. In 1930 Dr. Ersner became the first Temple graduate to be appointed a full professor in the School of Medicine. He also held appointments at the University of Pennsylvania Graduate School of Medicine and the former Mt. Sinai and Jewish hospitals, now the southern and northern divisions of Albert Einstein Medical Center.

Unit for Psychotherapeutic Treatment.—Dr. O. Spurgeon English, head of the department of psychiatry, announced the opening of a new 23-bed open floor unit at the Temple University Medical Center for the treatment of combined mental and physical ills. A program to promulgate the concept of a mental health check-up also is planned. Although geared primarily to psychotherapeutic techniques, adjunctive treatment in the new section will include the use of drugs and electroshock. Rooms have been outfitted in a modern decor, and day-beds in lieu of typical bedroom furniture carry out a modern sitting-room atmosphere. A solarium at one end of the floor will lend itself to occupational activities and group therapy. Dr. Harold Winn has been named director of the new section.

University Grants.—Medical research and training funds amounting to $2,272,775 were granted to the University of Pennsylvania in the first quarter of 1960, it was announced by Dr. I. S. Ravdin, university vice-president in charge of medical affairs. The grants, coming from the government, foundations, and private industry, support projects in the University School of Medicine, Graduate School of Medicine, School of Veterinary Medicine, School of Dentistry, and the Henry Phipps Institute. They represent new sums obtained during the three-month period ending March 31. Largest grant, in the sum of $700,000, came from the National Science Foundation to support a five-year study of energy transfer and conservation under the direction of Britton Chance, Ph.D., director of the Johnson Foundation for Medical Physics, of the School of Medicine.

TEXAS

Dr. Casberg Goes to India.—Dr. Melvin Casberg, Austin, son of missionary parents in India, became director of the Christian Medical College at Ludhiana, Northern India, in March, succeeding Dr. Eileen R. B. Snow, retired. Dr. Casberg was formerly dean of St. Louis University School of Medicine and vice-president of medical affairs, University of Texas. Ludhiana is one of the only two top-standard coeducational Christian medical colleges serving Southern Asia. The medical college and 350-bed hospital has a teaching staff of 74 men and women and ministers to some 60,000 patients yearly.

Dr. Busch Named Department Chairman.—Dr. Harris Busch, of Chicago, was appointed professor of pharmacology and chairman of the department of pharmacology at Baylor University College of Medicine in the Texas Medical Center, Houston. Dr. Busch, who takes up his new duties on July 1, comes to Baylor from the University of Illinois College of Medicine, where he has been professor of pharmacology since 1959. He was a Baldwin Scholar in oncology at Yale University, 1952-1955, and an American Cancer Society Scholar in Cancer Research in 1955. He is a member of the Advisory Committee on Pathogenesis, American Cancer Society, and a member of the editorial board for *Cancer Research.*

WEST VIRGINIA

Medical School Dean Honored.—Dr. Edward J. Van Liere, dean of the West Virginia University School of Medicine, was honored at a special program at the Medical Center in Morgantown on May 12. Dr. Van Liere, who has served as dean for the past 25 years, will retire on June 30. Dr. Thomas L. Harris, of Parkersburg, president of the university board of governors, presided at the meeting which was held in the auditorium in the School of Medicine. Dr. Carl J. Wiggers, professor emeritus at Western Reserve University and David B. Dill, Ph.D., scientific director of medical research, Chemical Warfare Laboratories at the Army Medical Center in Maryland, presented papers. A special presentation was made of a check for $2,100 from Kanawha Medical Society for the student loan fund created in honor of Dr. Van Liere. The official name of the fund is the E. J. Van Liere Medical Student Loan Fund. A second gift of $887 from the Alumni Association of the School of Medicine increased the total amount in the fund to $10,000. This revolving loan fund is operated by the West Virginia Foundation for the benefit of students in the Medical School. Dr. Van Liere will continue to serve as professor of physiology at the Medical School.

GENERAL

Meeting of Tuberculosis Physicians.—On June 11, the annual meeting of the American Academy of Tuberculosis Physicians will be held at the Shore Club Hotel, Miami Beach, Fla. Twelve papers are scheduled for presentation. Guest speaker at the noon luncheon will be Dr. William F. Miller, associate professor of medicine, University of Texas Southwestern Medical School, Dallas, who will present "The Role of Tobacco Smoking in Diseases of the Respiratory Tract." The meeting will be concluded with a business session. For information, write Dr. George P. Bailey, P. O. Box 7011, Denver 6, Secretary.

Mental Disease Top Military Disability.—Mental disease is the top cause for physical disability retirements in the Navy and Air Force. This is revealed in a survey, conducted with the help of Army, Navy, and Air Force experts by the *Army Navy Air Force Journal*. In the Army mental disease ranks second to tuberculosis. Heart disease is a close third. In the Navy and Air Force, tuberculosis ranks behind mental illness and heart trouble. The study reveals a sharp reduction in the number of disability retirements in the Army, Navy, and Marine Corps, with a rise in such retirements among Air Force personnel.

Convention on Legal Medicine.—The American Board of Legal Medicine, Inc., will hold its annual convention June 12 at the Carillon Hotel, Miami Beach, Fla. Twelve papers are scheduled to be presented, including "Symptom Exaggeration, Malingering and Conversion Reaction: Psychological Complications of Orthopedic Disability," by Dr. Arthur M. Pruce, Atlanta, who is an invited participant. The annual business meeting will be held at 3:45 p. m., and the convention banquet at 8:30 p. m. will feature former U. S. Senator Claude Pepper, president, Dade County Bar Association, as guest speaker, presenting "The Doctor and His Influence on Public Matters." For information, write Dr. Harold Lefkoe, 1003-06 Medical Tower, Philadelphia 3, Secretary.

Art Exhibition in Miami Beach.—The 23rd annual art exhibition of the American Physicians Art Association will be held June 13-18 at the Miami Beach Exhibition Hall and Auditorium. More than 300 pieces of art will be on display. Created by physicians throughout the United States, the show will include oil paintings, water colors, drawings, sculpture, photography, and allied crafts. Three prizes and several wards of merit will be given in each of the categories of art media. The annual Garrison Parker Award for the "best work by a physician in practice not less than 5 years" will be issued. In addition, a popularity prize for the work best liked by the public will be selected by a popular vote. Dr. Thomas E. Newel, Dayton, Ohio, president-elect, will become the new president of the association. Headquarters of the American Physicians Art Association will be the Shore Club Hotel.

World Survey of Peptic Ulcer.—A world-wide survey of the differences in incidence and behavior of peptic ulcer is being undertaken under auspices of the World Organization of Gastroenterology, it was reported May 13 by Dr. Henry L. Bockus, Philadelphia, first chairman and a founder of the two-year-old international organization. The physician, recently returned from an extensive trip through Asia, the Middle East, and parts of Europe, is chairman of the University of Pennsylvania Graduate School of Medicine departments of medicine and gastroenterology. Peptic ulcer was chosen for the world-wide survey, Dr. Bockus said, because of "striking differences" in behavior patterns of this disease from country to country and also within a single country. Many of these epidemiologic—or environmental—variants have been noted before, he added, "but reasons for such differences have never been explained satisfactorily."

Meeting of Seaboard Group.—The 65th annual meeting of the Seaboard Medical Association of North Carolina and Virginia will be held June 17-19 at the Carolinian Hotel, Nags Head, N. C. The program includes the following speakers: Drs. Bernard J. Alpers, Jefferson Medical College; Ivan L. Bennett Jr., Johns Hopkins University; C. Donald Creevy, University of Minnesota; Garfield G. Duncan, University of Pennsylvania; John R. Heller, National Cancer Institute; Byrd S. Leavell, University of Virginia; Waldo E. Nelson, Temple University; Franklin L. Payne, University of Pennsylvania, Thomas B. Quigley, Harvard; John T. Sessions Jr., University of North Carolina; and Colin G. Thomas Jr., University of North Carolina. Four breakfast round-table discussions are scheduled for June 18. A panel discussion on infectious diseases is also planned. Exhibits and a social program are arranged. For information, write Dr. John L. McCain, Wilson Clinic, Wilson, N. C.

Symposium Published on Cell Culture Genetics.—"A Symposium on Cytology and Cell Culture Genetics of Man" has been published by the *American Journal of Human Genetics* with the aid of funds from the National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare. Reprints may be obtained upon request from Dr. Gordon Allen, Building 10, Room 2N208, National Institutes of Health, Bethesda 14, Md. The symposium is 42 pages in length and contains the following papers, originally presented in Pennsylvania Sept. 2, 1959: The Chromosome

Complements of Human Somatic Cells, by E. H. Y. Chu; Human Cytogenetics: Its Present Place and Future Possibilities, by C. E. Ford; Sexual Dimorphism in Interphase Nuclei, by M. L. Barr; Some Systems for the Genetic Analysis of Mammalian Cells, by L. Sachs and M. Krim; and Cell Cultures for Human Genetic Studies and Concluding Remarks, by M. Fraccaro.

Plan Study of Use of Maternity Facilities.—Seven national medical organizations will make a survey to determine the advisability and feasibility of using a portion of the obstetrical facilities in large cities for the care of gynecological patients, it was announced at the eighth annual meeting of the American College of Obstetricians and Gynecologists in Cincinnati. The purpose is to relieve the shortage of beds in other sections of a hospital. Cooperating with the college in the study will be the American Academy of General Practice, American Academy of Pediatrics, American Hospital Association, American Public Health Association, the Children's Bureau of the Department of Health, Education and Welfare, and the maternal health, nursing, and statistics sections of the United States Public Health Service. The project is made possible by a grant from the National Institutes of Health. A qualified epidemiologist will be selected to initiate the program and to direct the study on a full-time basis.

Annual Meeting on Nuclear Medicine.—The seventh annual meeting of the Society of Nuclear Medicine will be held at the Stanley Hotel, Estes Park, Colo., June 22-25. Over 70 speakers will present new scientific information covering research, medicine, and surgery as it concerns the use of nuclear phenomena in the diagnosis and treatment of disease. Special emphasis will be given to the diagnosis and treatment of thyroid disease, therapeutic use of radioisotopes, and "tools of the trade." The first annual address of the Nuclear Pioneers Series will be delivered by Edward Teller, Ph.D., of the University of California, in honor of the late Dr. Ernest O. Lawrence. The meeting is open to all physicians, veterinarians, nurses, physicists, technicians, and other scientists working with, or interested in utilizing, radioisotopes in the health field. There is a nonmember registration fee of $5. Registration forms and copies of the program may be secured by writing to Mr. Samuel N. Turiel, Administrator, Society of Nuclear Medicine, 430 N. Michigan Ave., Chicago 11.

Two Researchers Named Heart Investigators.—Manuel F. Morales, Ph.D., chairman, department of biochemistry, Dartmouth Medical School, Hanover, N. H., and Dr. Oscar D. Ratnoff, associate professor of medicine, Western Reserve University School of Medicine, Cleveland, are the eighth and ninth to receive research appointments from the American Heart Association to lifetime posts as career investigators. The awards become effective next July 1. The career investigatorship was originated by the association 10 years ago as an addition to its research program. The scientists selected for these posts are given a yearly award for life and have complete freedom to do research of their own choosing at any institution they wish. Dr. Morales is a native of Honduras and before accepting his present post at Dartmouth headed the physical biochemistry division at the Naval Medical Research Institute. Dr. Ratnoff obtained his M.D. degree at Columbia University. After completing a fellowship in medicine at Johns Hopkins University, he began his career as an instructor at that institution. He was appointed assistant professor of medicine at Western Reserve in 1950.

Northwest Proctology Meeting.—On June 22-24 the Northwest Proctology Society will hold its fourth annual meeting in Roche Harbor, Wash., at the Hotel De Haro. Dr. John L. McKay, Seattle, president of the society, will open the scientific program with an address, "The Progress of Proctology." Four panel discussions are arranged under the following titles and subtitles:

Adenomata of Rectum and Colon.
  a. Problems in Diagnosis.
  b. Criteria of Treatment.
Chronic Ulcerative Colitis.
  a. Medical Viewpoint.
  b. Surgical Viewpoint.
Anatomic Physiology of the Anorectum.
  a. Nerve Supply and Distribution: Muscles and Probable Function: Reflex Patterns.
  b. Physiology of Defecation and Continence; Relationship of Other Pelvic Structures.
  c. Unknown Factors.
Elective Surgery for Non-Malignant Diseases of the Colon.

For information, write Dr. Laurence D. Leslie, 1162 Willamette St., Eugene, Ore., Secretary-Treasurer.

Society News.—At the annual meeting of the **Industrial Medical Association** on April 27, the following officers were elected for the next fiscal year: Drs. Robert E. Eckardt, president, Linden, N. J.; Gradie R. Rowntree, president-elect, Louisville, Ky.; H. Glenn Gardiner, first vice-president, East Chicago, Ind.; John L. Norris, second vice-president, Rochester, N. Y.; Leonard S. Arling, secretary, Minneapolis; and Jermyn F. McCahan, treasurer, Chicago.——William B. Waddell, a Duke University medical student, has been elected national president of the **Student American Medical Association.** Mr. Waddell succeeds William Kirkland, of the University of Oklahoma Medical School. Other national officers elected for the coming year are Thomas H. Alt, of Indianapolis, vice-president; and Richard Goode, of the University of Southern California, treasurer.——The American Pediatric Society installed the following officers May 5-6: Drs. L. Emmett Holt Jr., New York City, president; Edward B. Shaw, San Francisco, vice-president; Conrad M. Riley, New York City, secretary-treasurer; Robert J. McKay Jr., Burlington, Vt., recorder (editor); and Warren E. Wheeler, Columbus, Ohio, member of council (for seven years). The 1961 meetings of the American Pediatric Society and the Society for Pediatric Research will be held at The Traymore, Atlantic City, N. J., May 2-5, with the American Pediatric Society sessions on the first two days and the Society for Pediatric Research the two last days.

Twenty Physicians Receive Residency Scholarships.—Twenty physicians received $1,000 scholarship awards March 22 to start their general practice residency training in July. The awards, presented by the American Academy of General Practice, were announced during the academy's 12th annual scientific assembly. The scholarship awards are designed to help defray the cost of general practice residencies and are from a fund established by Mead Johnson & Co., Evansville, Ind., Dr. Bernard E. Edwards, South Bend, Ind., chairman of the academy's Mead Johnson Awards Committee, announced the 1960 recipients. The winners, selected on the basis of "scholarship, professional aptitude, and fitness for general practice" are:

Drs. Richard D. Benjamin, St. Louis; Chandler S. Bethel, Wichita, Kan.; Watson A. Bowes Jr., Denver; Edward S. Bush, Canton, Ohio; Harry B. Campbell, West Monroe, La.; Joe T. Diffee, Little Rock, Ark.; Richard L. Dobbins, Washington C. H., Ohio; Robert H. Finley, Belleville, Mich.; Donald J. Flaster, Hempstead, N. Y.; Roy L. Gregory, Transylvania, La.; Ward B. Hurlburt Jr., Salt Lake City; Charles A. Keller Jr., New Orleans; Gerard P. Lukaszewicz, Athens, Ga.; Robert B. Monroe, Sioux Falls, S. D.; John B. Myers, Richmond, Va.; John R. Schafer, Sacramento, Calif.; Oren R. Smith Jr., Sanford, Fla.; Charles H. Stinnett, Horatio, Ark.; John A. Wagner, Tucson, Ariz.; William S. Warr, Opelika, Ala.

Awards Available for Arthritis Study.—The Arthritis and Rheumatism Foundation offers predoctoral, postdoctoral, and senior investigatorship awards in the fundamental sciences related to arthritis for work beginning July 1, 1961. Deadline for applications is Oct. 31, 1960. The program provides for three awards: (1) predoctoral fellowships, limited to students who hold a bachelor's degree, (2) postdoctoral fellowships, limited to applicants with the degree of doctor of medicine, doctor of philosophy, or their equivalent; and (3) senior investigator awards, made to candidates holding or eligible for a "faculty rank" such as instructor or assistant professor (or equivalent) and who are sponsored by their institution. Stipends range from $2,000 to $10,000 per year. A sum of $500 will be paid to cover the laboratory expenses of each postdoctoral fellow. An equal sum will be paid to either cover the tuition expenses or laboratory expenses of each predoctoral fellow. For senior investigators, an additional 10% of the stipend will go the institution to be applied to annuity programs, laboratory expenses, travel, etc. For information and application forms, address the Medical Director, Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19.

Rehabilitation Service for Iceland Hospital.—The services of a New York physician as a consultant in the development of rehabilitation services is being provided to one of Iceland's largest hospitals. The physician is Bruce B. Grynbaum, M.B., associate clinical professor, department of physical medicine and rehabilitation, New York University Medical Center. The hospital expanding its rehabilitation services is the "Landspitalinn." Dr. Grynbaum's services are being made available through the World Rehabilitation Fund and the International Society for the Welfare of Cripples. Dr. Grynbaum made his first consultation visit to Reykjavik on May 20-27. His visit to Iceland is part of a long-range program to strengthen rehabilitation services for the physically handicapped in Iceland through establishment of a physical medicine and rehabilitation service at the "Landspitalinn." The physician who will eventually direct the service, Dr. Hauker Thordarson, is currently undertaking postgraduate training in the Department of Physical Medicine and Rehabilitation, New York University Medical Center, under a fellowship from the World Rehabilitation Fund. Dr. Thordarson will complete his three-year training program and return to Iceland in January, 1962.

Medical Assistance Plan.—A Community Medical Assistance Program, which helps small towns plan and build a modern medical center that will help attract one or more physicians to the area, has been organized by the Sears-Roebuck Foundation. The foundation works with civic groups or the medical society to determine if there is sufficient economic potential for a physician to earn an annual net income of at least $15,000 and helps form a nonprofit corporation to raise funds for the building if there is a need for a doctor in the area. "Since the people hope to regain their investment in the corporation, they must support the new doctor," the foundation stated. "The doctor, therefore, not only gets a new low-rent building, but a built-in-practice." Blueprints, specifications, and architectural advice for the building are provided by the foundation. A prefabricated medical center, a two-doctor unit with 10 rooms, was the central exhibit at the recent meeting of the American Academy of General Practice in Philadelphia. This building can be erected anywhere in the country for $35,000. A one-doctor unit costs about $18,000. Once a physician agrees to practice in a certain medical center, the foundation provides the services of a professional consultant to help him obtain financial assistance, purchase equipment, and set up a sound financial records system. Additional information on the Community Medical Assistance Program, and how physicians may investigate the available opportunities in various sections of the country, may be obtained by writing the Sears–Roebuck Foundation, 3333 W. Arthington, Chicago.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	May 14, 1960		May 16, 1959 Total
	Paralytic Type	Total Cases	
New England States			
Maine	1	1	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	..	..	..
Rhode Island	..	..	..
Connecticut	..	..	..
Middle Atlantic States			
New York	..	1	..
New Jersey	..	..	4
Pennsylvania	..	..	..
East North Central States			
Ohio	2	2	1
Indiana	..	..	1
Illinois	..	..	..
Michigan	..	2	1
Wisconsin	1	1	1
West North Central States			
Minnesota	..	..	..
Iowa	..	..	1
Missouri	..	..	..
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	..	..	2
Kansas	..	..	2
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	..
West Virginia	..	..	..
North Carolina	..	..	..
South Carolina	..	..	..
Georgia	..	..	..
Florida	..	1	4
East South Central States			
Kentucky	..	..	1
Tennessee	..	..	1
Alabama	..	..	..
Mississippi	..	..	1
West South Central States			
Arkansas	..	..	2
Louisiana	..	..	..
Oklahoma	..	..	..
Texas	..	..	9
Mountain States			
Montana	..	..	..
Idaho	..	..	..
Wyoming	..	..	..
Colorado	..	..	..
New Mexico	..	..	..
Arizona	..	..	..
Utah	..	..	..
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	..	..	2
California	1	1	3
Alaska	..	..	..
Hawaii	..	..	..
Territories and Possessions			
Puerto Rico	..	..	..
Total	5	9	36

Society News.—At the meeting of the **Harvey Cushing Society,** April 14-16, the following officers were elected: Dr. J. Granfton Love, president, Rochester, Minn.; Dr. Leonard T. Furlow, president-elect, St. Louis; Dr. John E. Raaf, vice-president, Portland, Ore.; Dr. Hendrik J. Svein, secretary, Rochester, Minn.; Dr. Eben Alexander Jr., treasurer, Winston–Salem, N. C.; Dr. Louise C. Eisenhardt, historian, New Haven, Conn. The next meeting of the society will be held in Mexico City, April 17-19, 1961, with headquarters at the Hotel del Prado. The chairman of local arrangements for this meeting is Dr. Manuel Sanchez Garibay.——The new officers for the **American College Health Association** for 1960-1961 are as follows: president, Dr. Samuel I. Fuenning, Lincoln, Neb.; president-elect, Dr. Thomas V. Urmy, Williamstown, Mass.; vice-president, Dr. Lawrence W. Holden, Boulder, Colo.; and secretary-treasurer, Dr. Norman S. Moore, director of the Health Service at Cornell University, Ithaca, N. Y. The next meeting of this association will be held in Detroit April 26-29, 1961, at the Park Shelton Hotel.——At the annual meeting of the **North Pacific Society of Neurology and Psychiatry** the following officers were elected: president, Dr. Peter O. Lehmann, Vancouver, B. C.; president-elect, Dr. Robert S. Dow, Portland, Ore.; secretary-treasurer, Dr. Thomas H. Holmes III, University of Washington School of Medicine, Seattle 5; and executive committee, Drs. Edward K. Kloos, Portland, Wallace W. Lindahl, Seattle, and R. L. Whitman, Vancouver, B. C.

Foundation Reports Disbursements.—The Smith Kline & French Foundation gave $735,611 to more than 200 organizations throughout the nation for charitable, scientific, and educational purposes during 1959, it was disclosed April 26 in a report released by trustees of the foundation. The 1959 disbursements, largest yearly total ever given by the foundation, brought to $3,433,738 the amount awarded by the independent trust since is was established by Smith Kline & French laboratories, Philadelphia pharmaceutical firm, in December, 1952. The foundation also maintains two programs for the matching of gifts by employees of the pharmaceutical firm. On a dollar for dollar basis up to $2,000, the foundation equals donations by SK&F employees to universities, colleges, and secondary independent schools, and hospitals. The largest portion ($529,300) of the 1959 disbursements went to education, either in the form of direct grants or through donations for equipment or other educational facilities. General support of higher education was provided through grants to such established national organizations as the National Fund for Medical Education, the American Foundation for Pharmaceutical Education, and the United Negro College Fund. The problem of mental illness continued to be one of the foundation's principal areas of concern during 1959 as it disbursed $118,033 to institutions and organizations active in this field. The awards went mainly for the recruitment of professional personnel, to support research and education, and to increase the public's awareness of mental health problems.

New Members Named to Science Academy.—On April 26 the National Academy of Sciences announced the election of 35 new members on the basis of their "distinguished and continued achievements" in original research. Their election took place at the 97th annual meeting of the academy at its headquarters in Washington, D. C. The National Academy of Sciences is a private organization of over 580 scientists, dedicated to the furtherance of science and to its use for the general welfare. The academy was established in 1863 under a Congressional Charter signed by President Lincoln. Empowered to provide for all activities appropriate to academies of science, it is also required by its charter to act as an adviser to the federal government in scientific matters. Close ties have always existed between the academy and the government, although the academy is not a governmental agency. The new members include Dr. Robert Galambos, chief, department of neurophysiology, Walter Reed Army Institute of Research; Dr. Robert J. Huebner, chief, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases; Dr. Salvador E. Luria, chairman, microbiology committee, Massachusetts Institute of Technology; Theodore T. Puck, Ph.D., professor of biophysics and head of department, University of Colorado Medical School; Dr. Carroll M. Williams, chairman, department of biology, Harvard University; Dr. Clinton N. Woolsey, Charles Sumner Slichter Research Professor of Neurophysiology, Medical School and Graduate School, University of Wisconsin.

FOREIGN

Course in Nasal Surgery in Jerusalem.—A postgraduate course, "Reconstructive Surgery of the Nasal Septum and External Pyramid," will be presented by the department of otorhinolaryngology of Mayer de Rothschild Hadassah University Hospital and the Hebrew University-Hadassah Medical School of Jerusalem in Jerusalem, July 31-Aug. 11. The guest director will be Dr. Maurice H. Cottle, professor of rhinootolaryngology, Chicago Medical School, and founder of the American Rhinologic Society, which will cooperate in the presentation. Dr. Cottle will be assisted by a faculty of specialists from the United States and other countries. For information, write the Dean, Hebrew University-Hadassah Medical School, Jerusalem, Israel, or to Dr. Robert M. Hansen, Secretary, American Rhinologic Society, 1715 N. Wheeler Ave., Portland 17, Ore.

Geographical Pathology Meeting in London.—The seventh International Conference of the International Society of Geographical Pathology will be held at the Royal College of Surgeons of England June 28-30 on the subject of Eclampsia and Preeclampsia in Pregnancy, under the presidency of Prof. J. Henry Dible, London. Professor Dible will open the scientific program the morning of June 28 with introductory remarks. The program is arranged under the following major headings:

National Reviews of Eclampsia and Pre-Eclampsia.
International Reviews of Eclampsia and Pre-Eclampsia.
Morbid Anatomy of Mother, Child, and Placenta.
Clinico-Pathological Aspects of Eclampsia and Pre-Eclampsia.
Free Communications.

Simultaneous translations will be available in English, French, and German. The society is governed by an International Executive Committee of which the General Secretary is Prof. F. C. Roulet, of Basle, Switzerland. The conference dinner will be held June 29. For information, write the Prof. George Cunningham, Royal College of Surgeons, Lincoln's Inn Fields, London W. C. 2, England.

CORRECTION

Dr. Murphy Is Chancellor of the University of Kansas.—In an item appearing in the May 7 issue of The Journal, page 62, Medical News Section, it was erroneously stated that Dr. Franklin D. Murphy is presently chancellor of the University of Kansas School of Medicine. Dr. Murphy is chancellor of the entire University of Kansas. The present dean of the University of Kansas School of Medicine, Dr. W. Clarke Wescoe, has been appointed to fill Dr. Murphy's position as chancellor of the University of Kansas when Dr. Murphy becomes chancellor of the University of California at Los Angeles on July 1.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

Alabama: *Examination.* Montgomery, June 21-23. Sec., Dr. D. C. Gill, State Office Bldg., Montgomery.

Alaska:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

California: *Written.* San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:* *Examination.* Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Connecticut:* Hartford, July 13-14. Sec., Dr. Stanley B. Weld, 160 St. Ronan St., New Haven.

Delaware: *Examination and Endorsement.* Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:* *Examination.* Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:* *Examination.* Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Guam: *Subject to Call.* Act Sec., Dr. F. L. Conklin, Agana.

Idaho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 358 Sonna Bldg., Boise.

Indiana: *Examination.* Indianapolis, June 22-24. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Illinois: *Examination.* Chicago, July 12-14. *Reciprocity.* Chicago, July 15. Supt. of Registration, Mr. Frederic B. Selcke, Capitol Bldg., Springfield.

Kansas:* *Examination.* Kansas City, June 16-17. *Endorsement.* Kansas City, June 18. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

Maryland: *Examination.* Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Massachusetts: *Examination.* Boston, July 12-15. Sec., Dr. David W. Wallwork, Room 37, State House, Boston 33.

Minnesota:* *Special Written Examination.* Minneapolis, June 14-16. *Regular Written Examination.* Minneapolis, June 21-23. *Reciprocity.* Minneapolis, June 23. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Building, St. Paul 2.

Mississippi: *Examination.* Jackson, June 20-21; *Reciprocity,* Jackson, June 16. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Montana: *Examination and Reciprocity.* Helena, Oct. 4. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

Nebraska:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada: *Examination and Reciprocity.* Reno, Sept. 7 and Dec. 7. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

New Hampshire: *Examination and Reciprocity.* Concord, Sept. 14-17. Sec., Dr. Edward W. Colby, 61 South Spring St., Concord.

New Jersey: *Examination.* Trenton, June 21-24. *Reciprocity.* Continuously. Sec., Dr. Royal A. Schaaf, 28 West State St., Trenton.

New York: *Examination.* Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: *Examination and Endorsement.* Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 13-16. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: *Reciprocity.* Columbus, June 17. *Examination.* Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oregon:* *Examination.* Portland, July 12-13. *Endorsement,* July 14-16. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: *Examination.* Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

Rhode Island:* *Reciprocity.* Providence, June 23. *Examination.* Providence, July 7-8. Administrator, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

South Carolina: *Examination.* Columbia, June 28-29. Sec., Dr. Harold E. Jervey, Jr., 1329 Blanding St., Columbia.

South Dakota:* *Examination.* Rapid City, July 19-20. *Reciprocity.* Continuously. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

Tennessee:* *Examination.* Memphis, June 15-16. *Reciprocity.* Continuously. Sec., Dr. Alfred H. Mason, 1635 Exchange Bldg., Memphis 3.

Texas:* *Examination and Reciprocity.* Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: *Examination.* Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Vermont: *Examination and Reciprocity.* Burlington, June 16-18. Sec., Dr. F. J. Lawliss, Richford.

Virginia: *Examination and Reciprocity.* Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

Washington:* *Examination.* Seattle, July 18-20. *Reciprocity.* Continuously. Administration, Mr. Thomas A. Carter, Capitol Bldg., Olympia.

Wisconsin:* *Examination.* Milwaukee, July 12-14. Sec., Dr. Thomas W. Tormey, 115 So. Pickney St., Madison.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arizona: *Examination.* Tucson, June 21. *Reciprocity.* Tucson, Approximately June 25. Sec., Mr. Hirman E. Bateman, University of Arizona, Tucson.

Colorado: *Examination and Reciprocity.* Denver, Sept. 7-8 and Dec. 7-8. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

Connecticut: *Examination.* New Haven, June 11. *Reciprocity and Endorsement.* Continuously. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

Kansas: *Examination.* Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Minnesota: *Examination.* Minneapolis, June 7-8. *Reciprocity. Continuously.* Sec., Dr. Raymond N. Beiter, 105 Millard Hall, University of Minnesota, Minneapolis 14.

New Mexico: *Reciprocity.* Santa Fe, June 25. *Examination.* Santa Fe, July 17. Sec., Mrs. Marguerite Cantrell, Box 1522, Santa Fe.

South Dakota: *Examination and Reciprocity.* Vermillion, June 10-11. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Madison, Sept. 9. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

GOVERNMENT SERVICES

NAVY

Captain Graybiel Honored.—Capt. Ashton Graybiel, M. C., director of research of the U. S. Naval School of Aviation Medicine, Pensacola, Fla., in May was given the Admiral William S. Parsons Award for Scientific and Technical Progress. The award is presented each year to a naval medical officer. Dr. Graybiel was nominated for the award by Capt. Langdon C. Newman, M. C., commanding officer, U. S. Naval School of Aviation Medicine, in recognition of Dr. Graybiel's participation in recent biospace flights, and especially for his efforts as medical officer in charge of the now famous Able-Baker monkey flight, which has gained world renown for the Naval School of Aviation Medicine.

Safety Awards Go to Ten Hospitals.—Ten U. S. Naval Hospitals have earned the Secretary of the Navy Award for achievement in safety for the calendar year 1959. The hospitals were among 162 naval activities chosen for the award. Each of the hospitals selected has won the award previously, with the U. S. Naval Hospital on Guam receiving the award for the ninth time. Others winning the award were the U. S. naval hospitals at Bainbridge, Md., sixth time; Beaufort, S. C., seventh time; Bremerton, Wash., fourth time; Camp Pendleton, Calif., fourth time; Charleston, S. C., fifth time; Great Lakes, Ill., fifth time; Memphis, Tenn., fourth time; Philadelphia, sixth time, and Quantico, Va., sixth time.

MEND Symposium.—The first Medical Education for National Defense Symposium to be held in the San Francisco Bay Area was in April at the U. S. Naval Hospital, Oakland, with more than 100 deans and professors attending from medical schools throughout the country. The three-day program was devoted to the many phases of medical research in progress at Oak Knoll, Navy Medical Research Unit 1, Berkeley, Calif., the Navy Biological Laboratory, Naval Supply Center, Oakland, and the Navy Radiological Defense Laboratory at Hunter's Point.

FOOD AND DRUG ADMINISTRATION

Reporting Drug Reactions.—A program for the reporting of unusual or adverse reactions to drugs will be conducted in those hospitals which represent a cross section of medical specialties. As the program develops, additional hospitals will be included with the aim of establishing nationwide reporting. The project is an outgrowth of a voluntary pilot study carried out during the past four years in cooperation with the American Association of Medical Record Librarians, the American Society of Hospital Pharmacists, the American Medical Association, and the American Hospital Association. The program is designed to develop information promptly on the untoward effects of drugs, especially the newer drugs.

Prior to release for general use, new drugs must be evaluated from the standpoint of safety by the bureau of medicine of the Food and Drug Administration. Notwithstanding a most careful check of the submitted data, wide clinicial use may bring to light effects not apparent in the investigative studies. When these become known, appropriate measures are taken to afford a greater degree of protection for the patient. Remedial steps necessary on the part of the drug manufacturer or distributor may vary from a change in the labeling to inform physicians and others who are responsible for patient care to a removal of the drug from the market. The Food and Drug Administration has previously had to rely on the published literature and sporadic reports from physicians, institutions, and pharmaceutical manufacturers to supplement its own small staff in checking experience with new drugs.

Drug Seizures.—In March a soybean extract was represented as a source of pure lecithin, said to be needed by persons aged over 35 years and described as a "billion dollar meal" that would supply all the vitamins and minerals necessary to develop and maintain good health. It was further offered to regulate and lower the cholesterol level of the blood and to supply maximum biological benefit to the brain, nerve tissues, blood plasma, and cells of the body. The need for lecithin in human nutrition has not been established, and this product is worthless in the conditions for which it was offered.

Capsules of vitamin E were promoted as a treatment for preventing sterility in women, habitual miscarriage, menopausal symptoms, and persistent skin ulcers. No vitamin E supplementation is required, because this vitamin is adequately supplied by commonly available foods. In April a default decree for destruction of this product was entered by the Federal Court for the Western District of Washington.

A milk powder concentrate containing calcium, phosphorus, protein, and lactose was illegally offered as a treatment for intestinal disorders including *toxemia, stagnation,* and constipation. Three makes of capsules that contained an alleged appetite suppressant, phenylpropanolamine hydrochloride, which is not effective for controlling the appetite, were illegally offered for weight reduction.

DEATHS

Abrahamer, Isidor, Medical Director, U. S. Public Health Service, Toronto, Ont., Canada; Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, 1926; served a residency at the Unity Hospital in Brooklyn; medical officer in charge of U. S. Public Health Service activities at the consulate general in Toronto; served with the U. S. Public Health Service Quarantine Station in Staten Island, N. Y.; died April 9, aged 58, of ventricular fibrillation.

Adler, Paul Winston, St. Johnsville, N. Y.; Medizinische Fakultät der Universität, Vienna, Austria, 1925; interned at St. Peter's General Hospital in New Brunswick, N. J.; physician for St. Johnsville Central School District; associated with the Little Falls (N. Y.) Hospital, where he died April 2, aged 59, of myocardial infarction.

Avant, Frank Hughes, Rocky Mount, N. C.; Meharry Medical College, Nashville, Tenn., 1933; interned at George W. Hubbard Hospital of Meharry Medical College, Nashville, Tenn.; died in the Park View Hospital April 4, aged 57, of chronic agranulocytic leukemia.

Avery, George Mitchell, Palmyra, N. Y.; Syracuse University College of Medicine, 1948; interned at the Delaware Hospital in Wilmington, Del.; served a residency at the Syracuse University Medical Center in Syracuse, N. Y., and the Strong Memorial Hospital–Rochester Municipal Hospital, Rochester, N. Y.; certified by the National Board of Medical Examiners; associated with the Newark–Wayne Community Hospital, Newark; died April 10, aged 38, of cerebral vascular accident.

Barry, Edmund Ⓜ Washington, D. C.; Columbian University Medical Department, Washington, D. C., 1891; veteran of the Spanish-American War; served as a member of the Board of Police and Fire Surgeons of the District of Columbia; died in the Georgetown University Hospital April 10, aged 95, of cerebral thrombosis.

Bender, Cecil Kolb, Goshen, Ind.; Northwestern University Medical School, Chicago, 1934; interned at the Miami Valley Hospital in Dayton, Ohio; served as health officer of Elkhart County; associated with the Goshen Hospital and the Elkhart (Ind.) General Hospital; died April 7, aged 53, of acute coronary thrombosis.

Berends, Emmo Dietrich Ⓜ San Diego, Calif.; University of Louisville (Ky.) Medical Department, 1921; served on the staffs of the San Diego County General Hospital and the Mercy Hospital; died April 2, aged 63, of coronary thrombosis.

Bivings, William Troy, Atlanta, Ga.; University and Bellevue Hospital Medical College, New York City, 1899; an honorary staff member, St. Joseph's Infirmary, where he died April 11, aged 84, of cerebral thrombosis.

Bouza, Francis Edward, Hermosa, S. D.; John A. Creighton Medical College, Omaha, 1911; for many years practiced in White River; died in the Veterans Administration Center, Hot Springs, April 10, aged 80, of arteriosclerotic heart disease.

Brown, Lucien Melbourne Ⓜ New York City; Long Island College Hospital, Brooklyn, 1923; served on the staffs of the Harlem and Sydenham hospitals; died April 15, aged 65, of coronary sclerosis.

Burnett, Thomas Raynes, Mission, Texas; Southwestern University Medical College, Dallas, 1906; veteran of World Wars I and II; the Mission football field was named for him; died April 3, aged 77, of coronary thrombosis.

Butler, Leroy Jefferson Ⓜ Winston-Salem, N. C.; born in Clinton Dec. 25, 1890; Medical College of Virginia, Richmond, 1915; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; professor of pediatrics at the Bowman Gray School of Medicine of Wake Forest College; past-president of the Forsyth County Medical Society, Eighth District Medical Society, and the North Carolina State Pediatric Society; veteran of World War I; chief of the pediatric staff, North Carolina Baptist Hospital, where he died April 10, aged 69, of pneumonia, congestive heart failure, and cirrhosis of the liver.

Chabut, Vedal George Ⓜ Northville, Mich.; University of Michigan Medical School, Ann Arbor, 1940; interned at the Grace Hospital in Detroit, where he served a residency; served a residency at the William H. Maybury Sanatorium in Northville and the Herman Kiefer Hospital in Detroit; member of the American College of Chest Physicians, American Trudeau Society, and the American Academy of General Practice; served as health officer; chief of staff, Community Hospital; died in St. Joseph Mercy Hospital, Ann Arbor, April 4, aged 50, of pneumonia.

Clark, Elbert, Winnetka, Ill.; Rush Medical College, Chicago, 1916; veteran of World War I; served as assistant professor of anatomy at the University of Chicago; for many years practiced in Evanston, where he was on the staff of Evanston Hospital;

Ⓜ Indicates Member of the American Medical Association.

died in Scripps Clinic, La Jolla, Calif., April 16, aged 78, of acute tracheobronchitis and pulmonary emphysemia.

Clark, Ira Ross, Carnegie, Okla.; Washington University School of Medicine, St. Louis, 1909; veteran of World War I; died March 20, aged 84, of coronary occlusion.

Cloyd, Thomas David, Florence, Ala.; Chattanooga (Tenn.) Medical College, 1908; died in the Eliza Coffee Memorial Hospital April 5, aged 74, of cerebral hemorrhage.

Coberly, Lee J., Seattle; Kansas City (Mo.) Medical College, 1899; died March 21, aged 91, of chronic lymphocytic leukemia.

Collier, Miles Arnold, Wauchula, Fla.; Louisiana State University School of Medicine, New Orleans, 1936; medical superintendent and owner of the Wauchula Infirmary; died March 30, aged 50, of carcinoma.

Colmers, Franz Adolph, New York City; Friedrich-Alexanders-Universität Medizinische Fakultät, Erlangen, Bavaria, Germany, 1898; died in the Stamford (Conn.) Hospital April 12, aged 84, of carcinoma of the cecum.

Cooper, Alden Vernon, Lynn, Mass.; University of Vermont College of Medicine, Burlington, 1905; associated with the Union Hospital and the Lynn Hospital, where he died April 6, aged 81, of congestive heart failure.

Cummings, Charles Stearns Ⓜ Onset, Mass.; Boston University School of Medicine, 1889; founder and first chief of staff of St. Luke's Hospital in Middleboro; honorary member of the staff of Tobey Hospital, Wareham, where he died April 7, aged 94, of *bronchopneumonia and arteriosclerosis.*

Drummond, Fred Henry Ⓜ Kawkawlin, Mich.; Northwestern University Medical School, Chicago, 1920; past-president of the Bay County Medical Society; member of the American Academy of General Practice; associated with the Mercy Hospital and the General Hospital in Bay City, where he died March 31, aged 68, of progressive brain damage (right hemiplegia due to stenosis of carotid artery).

Duncan, William Adolphus, Russellville, Ky.; Vanderbilt University School of Medicine, Nashville, Tenn., 1903; veteran of World War I; retired from the regular Army Jan. 4, 1918; died in the Logan County Hospital April 3, aged 83, of carcinoma of the prostate.

Dunderman, Frank Victor Ⓜ Akron, Ohio; University of Wooster Medical Department, Cleveland, 1909; member of the American Academy of General Practice; formerly member of the city board of health; died in the City Hospital April 19, aged 75, of congestive heart disease.

Dynan, Nicholas Joseph, Cambridge, Mass.; College of Physicians and Surgeons, Boston, 1905; died in the Massachusetts General Hospital, Baker Memorial, Boston, April 8, aged 80, of carcinoma of the prostate.

Eby, Ida L. Ⓜ Warren, Ind.; University of Illinois College of Medicine, Chicago, 1919; died March 29, aged 78, of chronic brain syndrome with senility.

Flick, William Archibald, Keyser, W. Va.; Emory University School of Medicine, Atlanta, 1917; past-president of the Potomac Valley Medical Association; served as a member of the National Guard and retired with the rank of captain; died in the Hampshire Memorial Hospital in Romney April 4, aged 76, as the result of injuries received in an *automobile accident.*

Freund, Jules Thomas, Bethesda, Md.; born in Budapest, Hungary, June 24, 1890; Magyar Kiralyi Pazmany Petrus Tudomanyegyetem Orvosi Fakultasa, Budapest, Hungary, 1913; after service as a medical officer in the Austrian Army during World War I, returned to Budapest to serve on the faculty of the Royal University Medical School; in 1923 came to the United States, where he continued his career of research and teaching in Philadelphia and New York; since 1957 chief of the laboratory of immunology in the National Institute of Allergy Diseases; formerly chief of the division of applied immunology at the Public Health Research Institute in New York City; vice-president of the American Association of Immunologists in 1954 and president in 1955; chairman of the Federation of American Societies for Experimental Biology in 1956-1957; gave the Claude Bernard Lecture of the University of Montreal for 1955 and received the Bronze Claude Bernard Medal and an honorarium; in 1959 received the Albert Lasker Award for achievement in medical research; a pioneer in modern immunology research, and was noted for his work on adjuvants increasing the protective value of vaccines and on little understood mechanisms of allergy; his work provided methods used routinely in basic laboratory research by immunologists throughout the world; the significance of his discoveries in preventive medicine have been recognized as vital to several important medical developments; died in the Clinical Center of the National Institutes of Health April 22, aged 69, of cancer.

Fridline, Gaylord Delsher Ⓜ Ashland, Ohio; Boston University School of Medicine, 1931; past-president of the Ashland County Medical Society; veteran of World War II; county coroner; a member of the board of health and the Ashland City Police Pension Board; died April 11, aged 56, of a heart attack.

Fries, Irvin Augustus Ⓜ Wallingford, Pa.; Jefferson Medical College of Philadelphia, 1891; veteran of the Spanish-American War and World War I; died April 8, aged 98.

Funk, Ralph L. Ⓜ Topeka, Kan.; College of Physicians and Surgeons, Medical Department of Kansas City University, Kansas City, Kan., 1901; formerly associated with the Indian Service; died April 5, aged 81, of congestive failure.

Garrison, Frank Otis, Bath, N. Y.; University and Bellevue Hospital Medical College, New York City, 1899; died March 31, aged 88, of bronchopneumonia.

Gerber, Morris Jean Ⓜ Harrisburg, Pa.; Jefferson Medical College of Philadelphia, 1932; interned at the Harrisburg (Pa.) Hospital; veteran of World War II; on the staff of the Harrisburg Hospital, where he died April 6, aged 53, of coronary disease.

Girardin, Alphonse Louis Jr. Ⓜ Fort Myers, Fla.; Emory University School of Medicine, Atlanta, 1937; interned at the Grady Hospital in Atlanta; served a residency at the Henrietta Egleston Hospital for Children in Atlanta; specialist certified by the American Board of Pediatrics; fellow of the American Academy of Pediatrics; veteran of World War II; on the staff of the Lee Memorial Hospital; died in the National Institute of Health, Bethesda, Md., April 8, aged 47, of coronary occlusion.

Goldman, Jack Ⓜ Portland, Ore.; University of Oregon Medical School, Portland, 1928; died Feb. 25, aged 64, of acute coronary occlusion.

Grant, Lucile Ruffe Ⓜ East Grand Rapids, Mich.; University of Michigan Medical School, Ann Arbor, 1923; on the staff of the Blodgett Memorial Hospital; died April 3, aged 64.

Grove, Arthur Francis, Dell Rapids, S. D.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1910; fellow of the American College of Surgeons; for many years associated with the Dell Rapids Hospital; died April 1, aged 75, of coronary disease.

Haas, John Henry, Ada, Mich.; Detroit College of Medicine, 1909; died in Lowell April 11, aged 87, of arteriosclerotic cardiovascular disease.

Hamilton, William F. Ⓜ Detroit; Northwestern University Medical School, Chicago, 1911; formerly on the staff of Harper Hospital where he died April 1, aged 83, of ruptured abdominal aortic aneurysm.

Holcomb, John Winslow Ⓜ Grand Rapids, Mich.; University of Michigan Medical School, Ann Arbor, 1934; interned at St. Luke's Hospital in Cleveland; served as health officer for the city of East Grand Rapids; member of the American Academy of General Practice and the Industrial Medical Association; on the staffs of the Blodgett Memorial and St. Mary's hospitals; died April 14, aged 52, of bronchogenic carcinoma with metastases.

Hollingsworth, Israel Pemberton Pleasants Ⓜ West Chester, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1903; specialist certified by the American Board of Pathology; member of the American Rheumatism Association and the American Society of Clinical Pathologists; veteran of World War I; served on the staffs of the Chester County Hospital and the Memorial Hospital of Chester County; died April 3, aged 79.

Jaspan, Samuel Clemens Ⓜ Trenton, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1912; on the staff of the Mercer Hospital; died April 3, aged 70, of arteriosclerotic heart disease.

Kaufman, Samuel Isidor Ⓜ Chicago; Loyola University School of Medicine, Chicago, 1921; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; veteran of World War I; served as clinical associate professor of ophthalmology at Chicago Medical School; associated with the Cook County Hospital and the Mount Sinai Hospital, where he died April 22, aged 66, of acute myocardial infarction and arteriosclerotic heart disease.

Kyes, Edwin Stuart Ⓜ Gonzales, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1899; died in the Baton Rouge (La.) General Hospital March 10, aged 89, of carcinoma of the prostate.

Landham, Clarence Broughton, Chattanooga, Tenn.; Emory University School of Medicine, Atlanta, 1933; interned at the Georgia Baptist Hospital in Atlanta; past-president of the Tennessee Association for Retarded Children; associated with the Erlanger and Memorial hospitals; died April 5, aged 51, of myocardial infarction.

Leahey, George A., Lowell, Mass.; Harvard Medical School, Boston, 1892; specialist certified by the American Board of Ophthalmology; member of the American Ophthalmological Society; fellow of the American College of Surgeons; past-president of the Middlesex North District Medical Society; served as president of the medical staffs of St. John's and Lowell General hospitals; vice-president and a director of the Washington Savings Bank; died April 1, aged 90, of coronary occlusion.

Long, Carolyn Jeanne Ⓜ Austin, Texas; Meharry Medical College, Nashville, Tenn., 1950; interned at the Homer G. Phillips Hospital, where she served a residency; served a residency at the Harlem Hospital in New York City; died in Houston April 6, aged 32, of coronary occlusion.

McAtee, John Stephen Ⓜ Laguna Beach, Calif.; John A. Creighton Medical College, Omaha, 1910; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; past-president of the Los Angeles and Orange County Radiological societies; veteran of World War I; died in the Queen of Angels Hospital, Los Angeles, April 10, aged 71.

McCabe, James Stephen Ⓜ St. Paul; Louisiana State University School of Medicine, New Orleans, 1940; interned at the Charity Hospital in New Orleans; served a residency at the Hotel Dieu, Sisters Hospital in New Orleans, Little Company of Mary Hospital in Evergreen Park, Ill., and Northwestern Hospital in Minneapolis; specialist certified by the American Board of Obstetrics and Gynecology; veteran of World War II; served on the staffs of Ancker Hospital, Miller Hospital, St. Joseph's Hospital, and St. Luke's Hospital, where he died April 4, aged 47, of hepatic cirrhosis.

McGauvran, Theodore Edgar, East Chicago, Ind.; Manitoba Medical College, Winnipeg, Man., Canada, 1925; received a citation of distinction from President Franklin D. Roosevelt for his medical work during World War II; on the staff of St. Catherine's Hospital, where he died March 29, aged 58, of coronary thrombosis.

McMillan, V. Bruce Ⓜ Overton, Texas; Baylor University College of Medicine, Dallas, 1929; associated with the Overton Memorial Hospital; managing trustee of the Bruce McMillan Jr. Foundation; chairman of the board of the First State Bank of Overton; member of the board of trustees of Kilgore (Texas) College; died in Mother Frances Hospital, Tyler, April 11, aged 55, of cor pulmonale and pulmonary emphysema.

Magdsick, Carl C. Jr. Ⓜ Sioux Falls, S. D.; University of Chicago, the School of Medicine, 1943; interned at the Illinois Central Hospital in Chicago; served a residency at the Veterans Administration Center in Des Moines, Iowa; member of the American Society of Anesthesiologists; veteran of World War II; associated with the McKennan and Sioux Valley hospitals; accidentally drowned in the Big Sioux River near Canton March 30, aged 42, when a canoe in which he was riding capsized.

Meisel, Jacob Jesse Jr. Ⓜ Pittsburgh; Hahnemann Medical College and Hospital, Philadelphia, 1927; veteran of World War I; on the staff of the Shadyside Hospital; died April 10, aged 64, of coronary thrombosis.

Meyer, William, Herndon, Va.; Medical College of Virginia, Richmond, 1918; past-president of the Fairfax County Medical Society; veteran of World War I; served three terms on the town council; formerly director of the Citizens National Bank of Herndon; past-president of the Herndon Rotary Club; died in Arlington (Va.) Hospital April 5, aged 68, of cerebral hemorrhage.

Mills, Claude J., Greenville, Ohio; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; veteran of World War I; founder, original trustee, and staff member of the Wayne Hospital, where he died April 3, aged 77, of coronary occlusion and cerebral vascular accident.

Mistretta, Joseph, Brooklyn; Columbia University College of Physicians and Surgeons, New York City, 1913; served on the staff of the Columbus Hospital; died April 15, aged 75, of carcinoma of the stomach.

Moore, Kinchen Carl, Wilson, N. C.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1909; formerly practiced in Laurinburg and served as health officer of Scotland County; died in the Woodard-Herring Hospital March 17, aged 74, of congestive heart failure.

Moore, Lawrence Henry Ⓜ Orrville, Ala.; Medical Department of the University of Alabama, Mobile, 1901; named "Citizen of the Year" by the West Dallas Civitan Club; died March 26, aged 82, of generalized arteriosclerosis.

Mullins, George Elbert, Emerson, Ark. (licensed in Arkansas in 1903); died March 27, aged 86, of heart disease.

Newton, Charles Robert, Akron, Ohio; Western Reserve University School of Medicine, Cleveland, 1914; served on the staffs of the Akron City and Akron General hospitals; died March 10, aged 74, of carcinoma of the rectum with metastases.

Nomland, Ruben Ⓜ Iowa City, Iowa; Rush Medical College, Chicago, 1925; certified by the National Board of Medical Examiners and specialist certified by the American Board of Dermatology; member of the American Dermatological Association and the American Academy of Dermatology and Syphilology; professor and head of the department of dermatology at the State University of Iowa College of Medicine; Vice-Chairman, Section on Dermatology of the American Medical Association in 1956; associated with the University Hospitals; died April 13, aged 61, of coronary thrombosis.

O'Connell, George Albert, Colonel, U. S. Army retired, Anniston, Ala.; Medical Department of Tulane University of Louisiana, New Orleans, 1906; veteran of World War I; commissioned in the

Dr. Robert Wells Library

regular Army in 1920 and retired in 1947; for many years health officer for Cleburne and Calhoun counties; fellow of the American College of Surgeons; died in the Walter Reed Hospital, Washington, D. C., April 10, aged 76, of acute confluent lobular pneumonia, bilateral.

O'Connell, Patrick Benedict Ⓜ Gillespie, Ill.; St. Louis University School of Medicine, 1919; specialist certified by the American Board of Otolaryngology; veteran of World War I; served as examining physician on the Macoupin County Selective Service Board for many years; city health officer; associated with St. Francis Hospital in Litchfield; director of the Peoples State Bank; died March 27, aged 66, of massive coronary thrombosis.

Openchowski, Mieczyslaw, East Orange, N. J.; Dragomanov Institute, Kiev, Russia, 1914; served in the Balkans and in France with the Russian Army during World War I; formerly on the faculty of Columbia University College of Physicians and Surgeons in New York City; psychiatrist of New Jersey Courts; served on the staffs of the St. Barnabas Hospital and St. Michael's Hospital in Newark, where he died April 9, aged 68, of coronary embolism.

Parker, Joseph Willis, Rocky Mount, N. C.; Howard University College of Medicine, Washington, D. C., 1949; interned at the Freedmen's Hospital in Washington, D. C.; member of the school board; died April 10, aged 43, of injuries received in an automobile accident.

Perry, Gentz Ⓜ St. Paul; University of Minnesota College of Medicine and Surgery, Minneapolis, 1897; specialist certified by the American Board of Radiology; member of the Radiological Society of North America; veteran of World War I and was awarded the Croix de Guerre with palm; formerly resided in Evanston, Il.; died April 17, aged 90, of coronary thrombosis.

Porter, Robert Brastow, Quincy, Mass.; Harvard Medical School, Boston, 1902; formerly practiced in North Easton, Mass., where he was school physician for many years and served on the board of health and on the draft medical board during World Wars I and II and the Korean War; died April 1, aged 83, of heart failure.

Powe, Alexander McKee, New Orleans; University of Louisville (Ky.) Medical Department, 1915; member of the American Academy of General Practice; associated with the Illinois Central, Charity, Métairie, and Mercy hospitals, and the Montelepre Memorial Hospital, where he died March 31, aged 71, of acute pulmonary edema.

Rose, William Arthur, Carlsbad, N. M.; Tufts College Medical School, Boston, 1940; interned at St. Luke's Hospital in Pittsfield, Mass.; certified by the National Board of Medical Examiners; associated with Carlsbad Memorial and St. Francis Xavier hospitals; died March 16, aged 44, of coronary thrombosis.

Rothring, Howard E., Seymour, Ind.; University of Cincinnati College of Medicine, 1944; interned at Indianapolis City Hospital, where he served a residency; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; veteran of World War II; on the staff of the Jackson County Schneck Memorial Hospital; died March 27, aged 40, of myocardial infarction.

Seckel, Helmut Paul George, Chicago; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1925; specialist certified by the American Board of Pediatrics; member of the American Pediatric Society; professor of pediatrics at the University of Chicago; formerly assistant professor of pediatrics at the University of Cologne, Germany; died in the Woodlawn Hospital April 13, aged 59, of myocardial infarction.

Taylor, Arthur Hastings, Suffolk, Va.; Medical College of Virginia, Richmond, 1943; interned at the Medical College of Virginia, Hospital Division in Richmond; veteran of World War II and was awarded the Purple Heart with Oak Leaf Clusters; served on the staff of the Louise Obici Memorial Hospital; died March 31, aged 43, of a heart attack.

Thomas, Julius Graham, Greensboro, N. C.; Medical College of Virginia, Richmond, 1915; on the staff of the Piedmont Memorial Hospital; died April 1, aged 74, of coronary thrombosis.

Underwood, Eric Otto Ⓜ Waveland, Ark.; University of Arkansas School of Medicine, Little Rock, 1912; died in the Sparks Hospital, Fort Smith, March 21, aged 70, of acute pulmonary tuberculosis.

Vogel, Herman Eugene Ⓜ Springfield, Ohio; Eclectic Medical College, Cincinnati, 1913; died March 30, aged 69, of arteriosclerotic cardiovascular disease and diabetes mellitus.

Weber, Walter David, Union City, N. J.; Long Island College Hospital, Brooklyn, 1910; past-president of the Hudson County Medical Society; served as school physician in West Hoboken and as police surgeon in Union City; for many years on the staff of the Christ Hospital, Jersey City, where he died March 4, aged 72.

Wengraf, Isidore, Brooklyn; Medizinische Fakultät der Universität, Vienna, Austria, 1898; died March 6, aged 86, of arteriosclerotic heart disease.

Young, William Henry, Clarksville, Tenn.; Vanderbilt University School of Medicine, Nashville, 1893; died March 31 [illegible] dent.

FOREIGN LETTERS

BRAZIL

Differential Diagnosis of Jaundice.—The differential diagnosis between hepatogenic and obstructive jaundice continues to be a pressing problem despite the appearance of new liver function tests. When the jaundice is of long duration the interpretation of a battery of tests is difficult and the result of a single test is usually inconclusive. Dr. Henrique Elkis and co-workers of the São Paulo State University (*Rev. Hosp. clin.* 24:446, 1959) studied the diagnostic value of the quantitative levels of serum mucoprotein in 70 patients who were selected exclusively on the basis of the presence of icterus, a fact that distinguishes the Elkis work from that of most observers who have reported on patients with hepatic diseases.

The series included patients whose ages ranged from a few days to 72 years, distributed as follows: 16 had viral hepatitis, 17 had cirrhosis of diverse types, 13 had primitive or metastatic tumors of the liver or the biliary ducts, 16 had obstructive jaundice, and 8 had hemolytic icterus. The serum mucoprotein is a glycoprotein which is easy to isolate, well defined, and unstable; it can be measured by simple laboratory methods. It normally constitutes 1% of the total blood protein, but in some inflammatory or neoplastic diseases it may represent 15%. The normal mucoprotein level, expressed in milligrams of tyrosine per 100 ml. of serum, was 2.54. The average level of the serum mucoprotein for the five groups of patients was as follows: hemolytic jaundice, 2.78; hepatitis, 2.42; cirrhosis, 3.19; obstructive jaundice, 5.71; and malignant tumors, 6.78.

The difference between the levels obtained for medical jaundice (hemolytic icterus, hepatitis, and cirrhosis) and for surgical jaundice was highly significant. In patients with infectious hepatitis and cirrhosis the level was never higher than 3.6 mg. High levels, comparable to those observed in obstructive jaundice, were observed in leptospiral jaundice, thus offering us a valuable means for the differential diagnosis between viral and leptospiral hepatitis. In comparison with other laboratory resources for the diagnosis of jaundices the serum mucoprotein level determination, as a single test, presented the lowest percentage of false diagnoses. For this reason and from the fact that it is a simple laboratory test, the authors strongly recommended its routine use.

DENMARK

Tuberculosis in the Armed Forces.—Dr. P. Mourier (*Ugesk. laeger*, March 17, 1960) reported certain changes with regard to the behavior of tuberculosis in Denmark's armed forces between 1946 and 1958 In the first four years about 33% of the recruits given the tuberculin test had a negative reaction to it. In 1958 this percentage of negative reactors had fallen to 10, a fall reflecting the growing frequency with which the rising generation in Denmark had undergone BCG vaccination. Though it is not compulsory, 93% of the recruits examined during the period under review had taken it. The x-ray examinations of their chests revealed pathological changes in 5,063 cases, fairly equally distributed between tuberculosis (2,282 cases) and other diseases (2,781). For the whole period the incidence of tuberculosis was 0.09% with a fall to between 0.03% and 0.06% in the latter part of the period. In spite of this fall, tuberculosis is still far from being stamped out in Danish recruits.

Use and Abuse of Laboratory Tests.—Dr. T. K. With (*Nord. med.*, March 24, 1960) denounced the tendency of certain hospital physicians to take refuge in a multitude of laboratory tests as a short cut to diagnosis and the earliest possible evacuation of hospital beds. Sometimes it is a nurse rather than a physician who requests many needless laboratory examinations as a routine procedure. The worst offenders are the university hospitals whose staffs compete with each other in the issue of laboratory requests using the plea that they are essential to research. Microscopic examination of urine in a search for erythrocytes is often used instead of the comparatively simple chemical test for hemoglobin. The author concludes that no laboratory test can replace a complete history and thorough physical examination. A laboratory test is useless unless it is inspired by careful thought. It may be expensive, troublesome, and even dangerous for the patient. The laboratory must never tower over the clinician as the final court of appeal. There is only one such final court—the postmortem examination, and even it may fail us.

Epidemiology of Coronary Occlusion.—Dr. R. Friedberg and co-workers (*Danish M. Bull.* vol. 7, Feb., 1960) deplored the fact that the diagnosis of coronary occlusion does not have an independent number in the "International Classification of Diseases, Injuries, and Causes of Death" as devised

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The items in these letters are contributed by regular correspondents in the various foreign countries.

by the World Health Organization, and so comes to be classified with a group including arteriosclerosis cordis, insuffіcentia coronaria, and angina pectoris. For this reason it is difficult to calculate the true incidence of coronary occlusion among patients outside a hospital. Hospital cases, on the other hand, are well suited to such calculation because in 90% of the deaths in Danish hospitals the cause is verified by postmortem examination. The records of the Sunby Hospital, in which 10,585 patients were admitted to medical wards between 1952 and 1956, showed that 260 of these patients suffered from coronary occlusion. The diagnosis was confirmed by postmortem examination in 87 cases. The number of cases of coronary occlusion per 10,000 population in a certain district of Copenhagen was calculated. From this it was estimated that in Denmark, with a population of 4,300,000, about 9,000 cases of coronary occlusion occur every year.

FRANCE

Coronary Arteriography.—G. Arnulf (*Arch. mal. coeur*, no. 10, 1959) has perfected a method of coronary arteriography which is performed during cardiac arrest produced by an injection of acetylcholine. It is necessary first to determine the dose of acetylcholine required for a cardiac arrest of about 8 minutes (100 to 200 mg.). The patient is given a general anesthetic, the aorta is catheterized through the subclavian artery, and then the injection of acetycholine is given. As soon as cardiac arrest occurs the contrast medium is injected through the catheter and serial roentgenograms are made. The antidote for acetylcholine is atropine. The author did not encounter any complications arising from the cardiac arrest even in patients with coronary disease. The obliterations were demonstrated on the films by the absence of a coronary segment. The importance of this technique lies in the possibility of examining the coronary circulation and of recognizing the extent of the coronary obliterations for evaluation of eventual surgical treatment. Furthermore, it permits investigation of the coronary vasomotor activity and assessment of the value of anastomosis.

Warts and Condyloma Acuminatum.—J. Albert-Weil (*Rev. path. gén.*, 1959) used dyes to treat warts and condyloma accuminata. After trying various preparations he selected a staining substance from polyethylene glycol (10 Gm. of luxol fast blue A. R. N., which is an azo dye, 10 Gm. of luxol fast blue M. B. S. N., which is a blue from phthalocyanine, and 80 Gm. of polyethylene glycol 4,000). This mixture was applied locally once a day to flat warts for a period of 20 to 30 days and two or three times daily to hyperkeratotic warts for the same period of time. The results were excellent in all patients.

Gamma Globulin Histamine Compound for Asthma.—At the convention for respiratory diseases in Rennes in November, 1959, Barré and Danrigal presented the results of treating 50 patients who had asthma with a compound of gamma globulin histamine. In healthy persons there is a partial fixation of histamine on the gamma globulins, but in allergic patients histamine occurs free in the plasma. Moreover, the serum of a healthy person has a protective power and produces an antihistaminic immunity when injected into an allergic person. The authors used histaglobin, a gamma globulin and histamine compound. They gave one injection every fourth day for a total of three injections. Treatment with cortisone, an antihistaminic agent, was discontinued three weeks before the new treatment was started. Excellent results, with complete disappearance of the crises, were obtained in 22 patients; partial improvement was obtained in 14, and the treatment failed in 14. The improvement was slow and progressive.

G. Trinquet and A. Meyer (*Semaine hôp. Paris*, Nov. 30, 1959) treated a series of 60 patients who had asthma with gamma globulin derived from human placenta and combined with dichlorhydrate of histamine. The patients received three subcutaneous injections given at intervals of eight days. If lasting improvement was noted a booster injection was given six months later. The effect manifested itself three or four weeks after the first injection in 50% of the patients. Of those with frequent attacks of asthma more than 50% were cured or improved.

GERMANY

Hemolytic Form of Lymphatic Leukemia.—A. Beickert of Jena University (*München. med. Wchnschr.*, no. 46, p. 2067, 1959) stated that the course of chronic lymphatic leukemia is governed so much by the erythrocytes that the occurrence of anemia should receive the same attention as the leukocyte count. These anemias usually result from marked lymphatic metaplasia of the marrow. There is also a hemolytic component which often, but not always, is occult and leads to the formation of inferior erythrocytes in the pathological marrow. Occasionally it produces moderate icterus, while increase of erythropoiesis in the marrow and reticulocytosis are always absent, and the result of a Coombs test is negative. Also patients with severe anemia, marked hemolytic syndrome, and anti-erythrocytic antibodies (the true hemolytic forms of chronic lymphatic leukemia) are observed.

Beickert saw this form in 3 of 36 patients with chronic leukemia. All three died. The total death toll in the 36 patients was 19. The course of the disease was markedly shortened by the hemolytic complication. Lymph node swellings were not marked in those with this complication, but the spleen was always distinctly palpable. A discrepancy between the degree of splenomegaly and lymph node swellings appears to be characteristic of the hemolytic form.

The average hemoglobin level was 4.8 Gm.% and the erythrocyte count was 1,600,000 or about one-half the number found in noncomplicated lymphadenosis. Since the color index was in the normal range, iron deficiency did not play an obvious role. The reticulocyte count was greatly increased. This was an important indication of the hemolytic form. The total leukocyte count showed no difference between hemolytic and nonhemolytic patients. The reason for the eventual production of autoantibodies against the patient's own erythrocytes is still largely unexplained.

Treatment for the hemolytic form of chronic lymphadenosis consists of large doses of glucocorticoids. Failures are infrequent, but the results are not so good as, for example, in patients with idiopathic hemolytic anemia. When the adrenocortical steroid therapy fails, blood transfusions may be considered, but these may cause a severe hemolytic crisis. Transfusions should be avoided if possible, but when they must be given large doses of corticoid should be given at the same time. Extirpation of the spleen is successful only occasionally. Treatment for the underlying condition, especially x-radiation, should be suspended during a hemolytic crisis whenever possible.

Vitamin D Intoxication.—H. Schönenberg of Aachen (*Medizinische*, no. 47, p. 2255, 1959) reported that in Germany infants are given 10 or 15 mg. of vitamin D_3 on their first visit to the infant welfare center. This dosage is repeated several times in the first year so that the infant in that period receives 30 to 45 mg. Large doses, however, and, in sensitive children, even therapeutic doses, can lead to symptoms of intoxication. Premature infants are especially susceptible. The frequent hypothesis that premature birth, being associated with an increased risk of rickets, is an indication for larger doses of vitamin D may lead to severe or even fatal hypervitaminosis. Premature infants, 2 weeks old, should not be given more than 120,000 units of vitamin D_3. This dose, which is effective in controlling rickets, may be repeated when required.

Children with renal damage or thyroid hypofunction are hypersensitive to vitamin D. Symptoms of intoxication are anorexia and vomiting, gray pallid complexion, and renal and cerebral affections. The infants are apathetic, refuse to take any food, and often greedily drink tea. Their stools are infrequent and hard, unlike the stools of those with actual gastroenteritis. There is often slight albuminuria and moderate leukocyturia. In severe cases the nonprotein nitrogen level may be increased. Part of the excess calcium is excreted through the kidneys. These infants are often febrile. In addition to meningism and sensitivity to touch, there may be convulsions. Radiography often shows a provisional calcification zone and osteoporosis of the metaphyses. The electrocardiogram shows signs of myocardial damage. The first aim of treatment in intoxication is to stop further administration of the vitamin and any preparation the child may be taking. The infant's nutriment should be changed to mother's milk, since cow's milk contains about four times the quantity of calcium. Cortisone has been recommended for this condition.

Vitamin C for Alkali Burns in the Eye.—At the 62nd Congress of the German Ophthalmological Society in Heidelberg in October R. Krueger of Munich University stated that alkali burns in the eye are common and often lead to blindness. Since present modes of treatment are not satisfactory, he sought a means of neutralization. The author first determined the speed at which alkali and acid enter the eye by applying these substances to the cornea of enucleated swine eyes and continuously recording the pH concentration in the anterior chamber. A marked pH shift to alkalinity was observed in the anterior chamber within 20 minutes after application of sodium hydroxide, potassium hydroxide, or calcium hydroxide at room temperature. Ammonia migrated even more rapidly (two or three minutes). If acids at all penetrated the uninjured cornea, they did so very slowly. Even after 90 minutes no shift to acidity was seen. When the corneal epithelium was removed, acids entered the aqueous humor as rapidly as the hydroxyl ions. Alkalis first destroy the epithelium, and the acid ions then enter readily.

Various organic and inorganic acids were investigated for their capacity to neutralize alkalis. Ascorbic acid was found to be best. Within 5 to 10 minutes after the application of ascorbic acid solution the previously alkaline aqueous humor gave an acid reaction, and after 15 to 25 minutes it had regained its original pH value of 7.4. Tests on the eyes of living rabbits gave the same result, but the reaction proceeded even more quickly; the aqueous humor was alkaline eight minutes after application of the alkali, and it was again neutral in only five to eight minutes after application of vitamin C. Control tests (without vitamin C) showed little if any scarring in the vitamin C-treated eyes. These results prompted the use of ascorbic acid in treating lime burns in the human eye. After instillation anesthesia with a 5% cocaine solution, 0.3 to 0.8 cc. of vitamin C was injected under the conjunctival lesions. When the severity of the case required it, the injection was repeated once or several times. The injections improved the blood supply of the ischemic areas and cleared the corneal turbidity. Krueger believed that ascorbic acid was superior to other substances because it entered the burned tissue at the same speed as the other alkalies and had a greater neutralizing capacity.

INDIA

Rice Polishing Concentrate.—C. H. Chakrabarti and co-workers (*Indian J. M. Res.* 48:231 [March] 1960) stated that rice polishings have a high vitamin content but have not been used in human nutrition because of the high cellulose content. A concentrate of rice polishings, which contained all the vitamins in adequate amounts, was prepared. On analysis this concentrate was found to contain an appreciable amount of choline besides other members of the vitamin B_2 complex. As choline is known to be an effective lipotropic substance, the authors wondered whether the rice polishing concentrate could prevent the development of fatty liver induced by a choline-deficient diet.

A series of 50 albino rats was divided into five groups. Group 1 was given a choline-free basal diet; group 2, a basal diet containing 0.04 Gm.% of choline; group 3, a basal diet containing 0.12 Gm.% of choline; group 4, a basal diet containing 0.04 Gm.% of choline plus 15 cc. of rice polishing concentrate per 100 Gm.; and group 5, a basal diet containing 0.04 Gm.% of choline plus 30 cc. of the concentrate per 100 Gm. The animals were sacrificed periodically and their livers studied. The concentrate prevented the development of fatty livers in the rats in group 5. In those in group 4 it did not completely prevent fatty changes. It was also found that 0.04 Gm.% of choline in a choline-free basal diet was enough to prevent the development of hemorrhagic kidney lesions but was not effective in maintaining the normal liver lipid levels. The authors concluded that rice polishing concentrate could exert a choline-sparing action.

Dermal Loss of Iron.—R. Hussain and co-workers (*Indian J. M. Res.* 48:235 [March] 1960) said that an appreciable loss of iron due to sweating is likely to occur in hot, humid regions. They studied the loss of iron in insensible and in visible perspiration in healthy subjects. In 16 subjects the loss of iron due to insensible perspiration from the forearm and part of the upper arm was determined. Visible sweating was induced by heat in 35 subjects and the iron content of cell-rich and cell-free sweat determined. The average iron content of insensible perspiration from an area of 769 sq. cm. in an eight-hour period was found to be 2.1 mcg. The average minimum loss through insensible perspiration would thus be about 0.13 mg. per day, assuming that there is uniform sweating from all parts of the body. The loss of iron through insensible perspiration was, therefore, considered negligible. The average iron content of cell-rich and cell-free visible sweat was found to be 1.15 and 0.34 mg. per liter respectively.

This iron content was found to vary in the same person at different times. Although the amount of iron in cell-free sweat was always much less than in cell-rich sweat, it could assume significance in hot, humid regions. Most of the iron lost was primarily associated with desquamation, probably of cells lining the sweat glands. Loss of iron through the skin may, therefore, be a contributory factor in causing iron deficiency anemia in the tropics.

Plasma Iron and Stress.—Gupta and Kumar (*Indian J. M. Res.* 48:140 [March] 1960) had previously observed that hypoferremia was a consistent feature of acute and chronic infections and that an inverse relationship existed between the extent of hypoferremia and the degree of pyrexia. A variety of pyrogens caused lowering of the plasma iron level, but physical hyperthermia in animals did not cause such a lowering. Oral administration of iron to these patients did not restore the plasma iron to a significant level as it did in normal controls. To determine whether the hypoferremia was related to stress or to altered adrenocortical function, patients admitted for surgical treatment of some chronic infection, and adult albino rabbits were studied. The latter developed severe hypoferremia on receiving electric shock, and the average decrease in plasma iron level was 55%.

Plasma iron level estimations were made in five patients who had undergone major operations, and simultaneous eosinophil counts were made to assess adrenocortical activity. Twenty-four hours after operation the plasma iron level showed a fall associated with a decrease in the number of circulating eosinophils. These tended to increase in number by the fourth postoperative day. Injections of ACTH in rabbits, administered to induce adrenocortical hyperfunction, resulted in a significant decrease in the plasma iron level. As eosinopenia is a recognized manifestation of adrenocortical hyperactivity, the association of eosinopenia with hypoferremia in patients suffering from operative stress may be related to increased adrenocortical function. Hypoferremia followed such diverse stimuli as electric shock and invasion by an infective agent. The stress caused by these stimuli may in some way be responsible for the reduction in the level of plasma iron.

Intrapleural Pressure After Drainage of Ascitic Fluid.—P. N. Laha (*J. Indian M. A.* 34:161 [March 1] 1960) studied the modification in intrapleural pressure, after drainage of ascitic fluid, in 20 patients with portal cirrhosis. A certain time interval was allowed to elapse, as previous work had suggested the possibility of reversion to normal of altered pulmonary function resulting from compensatory emphysema after abdominal paracentesis. The diagnosis of compensatory emphysema in these patients was based on clinical and radiologic findings. Modification in intrapleural pressure after paracentesis after 72 hours was seen in only 50% of the patients. It did not depend on the age of the patient, the duration of ascites, the degree of emphysema, or the amount of ascitic fluid drained. More than one factor could therefore be responsible for causing compensatory emphysema in patients with ascites due to portal cirrhosis.

SWEDEN

"Echo Sounder Pen."—An instrument for diagnosing internal diseases by means of sound waves was developed by Drs. C. Hellmuth Hertz and Inge Edler, of Lund University. The instrument, which is the shape and size of a fountain pen, emits ultrasound waves, the echo of which is picked up by another apparatus. The latter registers the findings as a curve on a paper tape. The pen-like instrument is placed on the chest or abdomen of the patient. The new method, which has been used with success in about 1,000 cases, is able to furnish information about the shape and movements of the various chambers of the heart and parts of the stomach that are not accessible to the usual methods of diagnosis, such as x-rays. Previously it had been necessary to make probing operations in order to diagnose with accuracy certain complaints in the stomach and the heart.

Stricter Control on Quacks.—New bills which concern the right to practice medicine have been placed before the Parliament. Among other things, they propose tighter rules against quackery and against the unauthorized use of the titles Doctor or Surgeon. The Minister of the Interior recommended a law to safeguard the right of the legitimate physician and another one to regulate the "quack" physician, including his advising patients by correspondence. Both laws are to be effective as of July 1, 1961. Under the Physicians Law, the requirement of holding Swedish citizenship has been abolished, and a medical degree obtained elsewhere than in Sweden but duly supplemented in Sweden will be considered as equivalent to a Swedish doctor's degree. Limited authorization can also be granted, either restricted to simpler professional tasks or geographically confined to areas bordering on Finland and Norway. A special clause prohibits a physician from advertising that he is a specialist unless he has been granted this right by the government or by the board of health.

The "Quackery Law" will apply to nonphysicians who, for a fee, examine the state of health of other people or treat them for illness. Nurses, medical gymnasts, and midwives are excluded. Diseases which may not be treated by quacks have been extended to include diabetes, epilepsy, or pathological conditions in conjunction with pregnancy or delivery. The quacks may not examine or treat children under the age of 8 years.

Medical Care Program.—Two of the main goals of the sweeping medical-care program submitted to the Swedish Parliament were that persons in need of special care for chronic diseases should not have to travel far in order to obtain the best possible treatment and that they should not have to wait long to be admitted to hospitals. Sweden will be divided into seven medical-care districts where facilities will be improved and expanded until eventually all medical specialties are represented. Each of the seven districts will then contain departments for neurosurgery, neurology, thoracic surgery, cardiology, plastic surgery, urology, pediatric surgery, cancer, and dermatology. All the centers will have heart-lung machines, artificial kidneys, and other modern equipment.

Liability to Infections After Splenectomy in Childhood.—Broberger and Gyulai (*Nord. med.*, Feb. 25, 1960) made a follow-up study of 470 children who in the past eight years had undergone splenectomy for such disorders as thrombocytopenia and rupture of the spleen. Serious postoperative infections had overtaken 4.5% of the children operated on after the age of one year, whereas this was the case with 22.5% of those operated on during the first year of life. The electrophoretic examinations made in 20 patients showed no pathological changes, and none of the 32 children whose serums were examined with reference to their bactericidal qualities showed any significant differences from normal. Judging by their own experiences and the literature on the subject, the authors concluded that the risk of infections among children who had a splenectomy after the age of one year is relatively small. This may not, however, apply to the children whose serious basic disease did not respond satisfactorily to splenectomy.

Imipramine for Mental Depression.—Dr. Lassenius and co-workers (*Svenska läk-sällsk. förhandl.*, Feb. 26, 1960) used imipramine to treat 52 women and 13 men who had mental depression. About half of these were over 50 years of age. Given at first by injection, the drug was later administered in tablet form, and the usual maintenance dose (between 75 and 150 mg.) was given daily for from one to six months. Among the 65 patients were 27 who became symptom-free and 14 who were improved. The best results were achieved in patients with endogenous depression, and 16 of the 19 patients in this group became symptom-free. The 34 patients who were allowed to continue this treatment under ambulatory conditions were not given more than 200 mg. daily and were kept under close supervision. Nearly all the patients complained of dryness of the mouth and sweating, particularly when taking large doses. Lassitude was common, and there were some complaints of constipation and disturbances of micturition, notably in older men.

Ultrasound Testing in Obstetrics and Gynecology.—Dr. B. Sundén of Lund (*Svenska läk.-sällsk. förhandl.* March 11, 1960) stated that ultrasound tests promise to yield useful information with regard to the viability of a fetus when abortion is threatened. His first tests were carried out on women who had qualified for the legal induction of abortion. Later the same tests were used to detect gynecologic tumors. (It is generally agreed that it is impossible by palpation alone to distinguish between a cystic and a solid swelling.) With the frequencies and length of exposure used in Lund, no harm has as yet been noted as resulting from these tests, but it must be admitted that, however encouraging the preliminary results may be, these tests are still in the experimental stage.

UNITED KINGDOM

Venereal Disease Program on Television.—A commercial television network put on a 45-minute program dealing with venereal disease. The *British Medical Journal* praised the efforts of the company concerned for trying to educate the public about a serious and growing health hazard and compared the presentation favorably with some of the sensational operating-room scenes that have been televised in the past. The program was described as successful and imaginative. It dispelled the old idea that health education is dull and unsuitable for presentation to the masses. Two weeks before the telecast, the *British Medical Journal* drew attention in its supplement to the mounting tide of new cases of gonorrhea and to the need for a public propaganda campaign to promote the prevention and treatment of venereal disease, particularly among the young. The telecast succeeded in doing this. "Patients" took part in the television program and related personal histories. These portrayals illustrated the general ignorance on the subject. It was pointed out that venereal disease is a far greater problem than poliomyelitis, which has received so much attention in the last few years.

Human Contraband.—Smuggling across the Malacca Straits from Sumatra to Malaya is an old custom. The commonest articles of contraband are cigarettes and illicit drugs, but customs officials have recently come across an innovation—the smuggling of lepers. Lepers cannot get effective treatment in Sumatra. Malaya, on the other hand, has some first-class leper settlements. About 50 Indonesians from Sumatra, who were smuggled into Malaya, are now under treatment at such a settlement near Kuala Lumpur. An organized band of smugglers bring these lepers across the Straits to a small island near Port Swettenham and then smuggle them ashore.

Dangers of Aspirin Exaggerated.—A number of reports have stated that aspirin can cause gastric erosions and bleeding, with consequent anemia, and sometimes massive gastrointestinal bleeding. Others believe that aspirin may produce chronic dyspepsia and precipitate a peptic ulcer. Baragar and Duthie (*Brit. M. J.* 1:1106, 1960) made a study extending over six years on 244 patients with rheumatoid arthritis who took aspirin regularly to relieve their pains. Of these patients 25% took from 8 to 12 0.3-Gm. tablets daily. Hemoglobin levels were determined at the beginning of the study and regularly thereafter, and detailed information was kept on the incidence of dyspepsia and peptic ulcers. Over the six-year period the patients, as a whole, showed an increase of 10% in their hemoglobin level, suggesting that if any gastrointestinal bleeding occurred it was not important and could not have been sufficient to cause anemia. In 75.8% the hemoglobin level at the end of the study was within 20% of that at the beginning, and in 22.6% it increased by 20%. It decreased in only four, or 1.6%, of the patients. Only three, or 1.2%, developed clinical or radiologic evidence of a peptic ulcer while taking aspirin. This figure is less than the incidence of peptic ulcer in the population as a whole. The incidence of dyspepsia in the arthritics was 12.3%, which is also within the accepted incidence for this condition in hospital patients.

The authors concluded that, as most arthritics can tolerate aspirin without any side-effects or evidence of anemia, the dangers of causing a peptic ulcer or precipitating gastrointestinal hemorrhage appear to have been greatly exaggerated.

CORRESPONDENCE

TREATMENT OF BRUCELLOSIS

To the Editor:—In the council report, "Current Status of Brucellosis in Human Beings" in The Journal, Feb. 13, page 697, Dr. Spink made erroneous statements which, unless corrected, will detract from the general knowledge of brucellosis. While it is true that the diagnosis of brucellosis is doubtful unless agglutinins are present in the blood in high titer or unless cultures yield the organism, it is not true that the absence of such laboratory data rules out active brucellosis.

Blood cultures show positive results in only about 33% of patients with acute brucellosis, even when the best cultural techniques, which seldom are available in either hospital or private laboratories, are used. When the illness is chronic, it is rare for the organism to be recovered from blood, for this phase of the illness is not bacteremic. It is only during the acute or subacute exacerbation of the chronic illness that the organism even occasionally can be recovered. McVay and co-workers (*Am. J. Path.* 25:776, 1949) and others have shown that culture of tissues such as spleen, lymph nodes, prostate, and oviducts may yield the organism in the acute or chronic illness, but such cultures are hardly a practical approach to diagnosis.

It should be clearly understood that positive culture is definitive proof of brucellosis but that negative cultural results must be ignored as they are without significance. Similarly, one cannot depend on agglutination reactions in high titer in diagnosis. Agglutinins in titers of 1:100 or above are uncommon in chronic brucellosis; in more than one-half of such illnesses the agglutination titer is negative or positive only in titers below 1:80. Antibiotic therapy is a source of further diagnostic difficulty. Undiagnosed febrile illnesses often are treated with broad-spectrum antibiotics, which results in suppression of agglutinins or circulating Brucella organisms or both. In short, Dr. Spink's comments on the agglutination test and culture accurately apply only to the acute illness or to acute exacerbations of the chronic illness.

Exception also must be taken to Dr. Spink's comments with respect to the skin test. Although it is true that "a positive test does not connote active brucellosis," it does indicate a clinical or subclinical past infection with Brucella and not simply exposure to it. It also points to the need for careful appraisal of other laboratory and clinical evidence which may suggest the existence of active brucellosis.

A test with negative results is a strong indication that brucellosis is not present and never was, although occasionally positive culture or high agglutination titers will be found in the presence of a skin test that gives negative results. One must be sure, however, that the skin testing antigen is an effective one; Brucellergen, although commonly used, gives negative reactions in about half of those patients who exhibit positive results when killed whole Brucella organisms are used.

It is wrong to state categorically that brucellosis is a self-limited disease. After an acute attack, the patient may remain well for a lifetime, but, as in tuberculosis, it is probable that the organism is not eradicated but rather that it lives in tissues such as lymph nodes, spleen, prostate, or oviducts in a state of quiescence. Exacerbation of active illness or of allergic manifestations of infection may occur at any time. Recurrence over a period of many years of more or less severity is the rule rather than the exception, unless treatment has been successful.

The following ambiguous statement appears in the report. "Brucellosis may have a severe impact on the nervous system. Weakness and mental depression are common manifestations. An emotionally unstable person may be plunged into a severe depression after an acute Brucella infection. He may be mistakenly subjected to anti-Brucella therapy for several years instead of having efforts directed toward the correction of the underlying psychosomatic disturbance." Is the underlying disturbance a psychosomatic one or is it the direct result of neurobrucellosis, which indeed Dr. Spink implies in the next sentence? Must the patient be emotionally unstable to suffer from neurospsychiatric manifestations of brucellosis? By no means has this been demonstrated. The careful and competent diagnostician does not treat psychosomatic illness for several years as if it were brucellosis. If he does make such an error, which indeed occasionally is inevitable, it is discoverable early.

Dr. Spink restates his opinion with respect to Brucella vaccines, saying that "there is no general agreement concerning their value." It is true that clinicians who have had little or no experience with this method of desensitization and relative immunization are skeptical or just do not believe in it for obscure reasons, but the vast majority of clinicians who are experienced in the treatment of chronic brucellosis believe that it is the best method.

It is wrong to say that vaccines are used for long periods of time. The usual duration is six to eight weeks, possibly with repeated courses at long intervals, depending on whether or not relapse occurs. No experienced clinician uses vaccine for the treatment of acute brucellosis, as Dr. Spink states. It would indeed be foolhardy as well as unnecessary, since broad-spectrum antibiotics are so effective in this phase of the illness.

Evidence has been on hand for years that vaccine therapy is the treatment of choice in chronic brucellosis for desensitization and immunization. Response to antibiotics in this phase of the illness is unsatisfactory in at least 50%. If diagnostic criteria such as those advocated by Dr. Spink are adopted most chronic cases will be missed. The use of a more realistic combination of clinical and laboratory data can keep diagnostic error to a minimum.

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The above comment was referred to the author of the article, and he has submitted the following reply.

To the Editor:—In reviewing the current status of the therapy of human brucellosis at the request of the A. M. A. Council on Drugs, I used not only the results of our own experience but also the reports of the committee on brucellosis of the National Research Council and of the expert committee on brucellosis of the World Health Organization. Since many investigators of human brucellosis do not agree with the opinions of Dr. Harris on the diagnosis and treatment of chronic brucellosis, a brief note of explanation is in order concerning the basis for this disagreement.

Most authorities agree that acute brucellosis occurs much more commonly than chronic brucellosis if one adheres to dependable diagnostic criteria, including serologic and bacteriological data. Dr. Harris also agrees that these rigid criteria should be used in the diagnosis of acute and subacute brucellosis. Furthermore, he states that brucella vaccine should not be used in the treatment of acute and subacute cases, but when he takes up the problem of chronic brucellosis he abandons the more precise approach to diagnosis and relies on the brucella skin test. The crux for his disagreement with other clinicians resides in the interpretation of the skin test. The brucella skin test is not a reliable diagnostic procedure, and vaccine therapy is of dubious value.

The committee on brucellosis of the National Research Council reviewed the available evidence on the skin test as a diagnostic tool and listened to the opinions of many observers, including those of Dr. Harris. The committee then reached the following conclusions about the diagnosis of brucellosis. "The only absolute proof for the diagnosis of brucellosis is isolation of Brucella from the patient. A presumptive diagnosis can be reasonably, though not absolutely, confirmed by the results of the agglutination test if the titer is 1:320 or higher. The dermal sensitivity test is of no aid in the diagnosis of a suspected case of brucellosis. Its indiscriminate and uncritical use has resulted in confusion among clinicians. The use of this test in clinical medicine should be abandoned." (Spink and others: *J. A. M. A.* 149:805 [June 28] 1952.)

Subsequently, the WHO expert committee on brucellosis considered this same problem on a world-wide basis and stated that "A positive intradermal test denotes a specific allergic condition of the individual and should be regarded as free from other diagnostic significance, regardless of the antigen or technique employed; it certainly does not prove the presence of an active infection" (WHO Technical Report Series, no. 67, Geneva, May, 1953). I suggest that the inquiring physician read the discussion in *Lancet* (Jan. 30, 1960, p. 263; Feb. 13, 1960, p. 390; Feb. 20, 1960, p. 439). A current polemic on the diagnosis of chronic brucellosis has been stirred up in England which indirectly involves Dr. Harris.

There is no question in my mind that brucellae can invade the tissues of animals and man and persist for many years, but this does not necessarily indicate the presence of active disease nor is this host-parasite relationship unique for brucellosis. Such relationships occur with other bacterial, fungal, rickettsial, and viral infections. Furthermore, there is no doubt that the symptoms of brucellosis can endure for several years, but it has been shown on the basis of reliable serologic and bacteriological data that this group comprises a relatively small number of patients.

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LEAF PROTEIN

To the Editor:—In his report, "World Population and Food Supply," in The Journal, April 9, page 1647, Dr. Warren Thompson discusses the obvious aspects of world food supply. He views critically the usual solutions that are offered when national food shortages come up for discussion: expansion of the tilled area in the world; increase of crop yields through improved agricultural methods; more effective redistribution of food surpluses from the United States, Canada, and other more fortunate countries; and control of population increases by promoting the use of contraceptive practices.

It is appropriate, therefore, to call attention to a report entitled "Leaf Protein as a Human Food" (Pirie: *Lancet,* Nov. 28, 1959, p. 961), that deals with investigations demonstrating that leaves can provide proteins valuable as human food.

The author believes that, with the methods he proposes, progress can be made toward solving the problems of food shortage without expensive or elaborate organization. He believes that this is a worthy area for research. An editorial in the same issue of *Lancet* gives some support to his contention.

Subsequent to publication of the previously mentioned report, comments from readers were published in the correspondence section of *Lancet:* Williams and Allen (Dec. 12, 1959, p. 1091) report separately that in various countries consumption of leaves is already an established practice; Bender (Jan. 9, 1960, p. 110) comments on the need for making an edible product that would become more acceptable than leaf protein products probably would; Guha (March 26, 1960, p. 704) tells of the advances that have been made in India relative to the possibilities of developing leaf proteins on both domestic and industrial scales.

This information is provided in the hope that investigators in this country may be stimulated to mobilize their skills and resources to provide an answer that would bring relief to the underprivileged areas in the world. In the long run, such work would be much more effective than direct financial or material subsidization for these areas, which at best affords only temporary relief.

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FFRANGCON ROBERTS

To the Editor:—I was interested in the source of the given name of Ffrangcon Roberts, the author of "Medical Terms," mentioned in the editorial, "Neologopoiesis," in The Journal, May 28, page 376.

J. A. T.
New York.

I too was interested, so I wrote to Dr. Roberts who replied in the following way.—Ed.

"Ffrangcon is a Welsh name. Nant Ffrangcon is a beautiful pass through the Snowdon range in North Wales. Ffrangcon means 'beavers,' therefore 'the valley of the beavers.' The double F is because in Welsh a single F is soft like V and two F's form a single letter pronounced like the English F. I was born in a small quarrying town called Bethesda at the entrance to the pass. In the same place was born David Ffrangcon Davies, the leading tenor of Victorian times. My mother, being very musical and an admirer of the singer, decided to give me the same Christian name."

Ten days later the following revision was received.

"Since I wrote to you I have had the opportunity of consulting Sir Ifor Williams, one of the greatest Welsh scholars. He assures me that the explanation which I gave you was incorrect. The true explanation is more interesting. The Franks were, of course, the Germans who invaded France and gave the country its name. A Welsh manuscript of the 12th century states that in the 8th century, a Welsh chieftain imported a body of these Franks, employing them as mercenaries and housing them in the valley. They came to be known as the Ffrancon, 'on' being the plural suffix and the F being duplicated to make it hard, not soft like a V. The G was inserted because, Welsh being a phonetic language, one cannot pronounce 'nc' (hard C) without sounding a G in between. Hence 'Ffrangcon.' I am grateful to you for having stimulated me to discover the true meaning of my name and to correct a lifelong error."

THE STEMMA OF HARVEY

To the Editor:—There was just one little oversight in your fine and definitive description of Padua (*J. A. M. A.*, March 26, p. 1393). You neglected to mention the stemma of William Harvey in the atrium.

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The reference to stemma was completely baffling until the following statement was discovered in a book of essays by Ruth Fox entitled "Great Men of Medicine" (New York, Random House, 1947). "In 1602 Harvey left Italy and returned to England. He had made himself a name at the University. It was customary to install tablets called *stemmata* around the fessors and students. Harvey's *stemma*, a white-clad walls of the building to commemorate important proarm holding a candle entwined by a snake, is a little worn with the passage of three hundred and fifty-odd years, but it is still to be seen in Padua." (It is only slightly less baffling now).—Ed.

PSYCHOTHERAPY AND ALLERGY

To the Editor:—It is curious that belief in the somatic cause of allergic disease, authenticated by carefully controlled studies through several decades, must be defended against the largely unsupported idea that its causes are mainly psychiatric. The article entitled "Psychotherapy" by Kenneth E. Appel, in The Journal, March 26, page 1343, is not only characteristic of this paradox but suggests that papers which consider psychiatric subjects need be far less critically constructed than those dealing with organic disease. I refer especially to

Dr. Appel's illustrative case of eczema and asthma. Not only must one assume that the diagnosis is correct, but the results are dismissed with the following statement. "She got well, and I think I had something to do with her recovery." I doubt whether any specialist other than a psychiatrist could be so blandly assumptive and escape the smirks of his colleagues.

I have yet to find any psychiatrists who have taken the trouble to study allergy. If they had, they would know of occasional spontaneous remissions for curious reasons—some known, some unknown. They would learn that hyperventilation has been mistaken for asthma and dermatitis facticia for eczema. They would also learn that people with allergies may be emotionally disturbed but are more usually normal and that these phenomena can only be equated with allergic disease when the intense fatigue of dyspnea or sleepless nights of scratching disturb the most stolid psyche. I become most concerned when the emotionally stable patient, intrigued by the claims of psychiatry, postpones treatment based on a proved diagnosis in favor of a will o' the wisp. I take no issue with Dr. Appel's general remarks, but his presentation of this case perpetuates the misconception that all is organically right and emotionally wrong. This informal assumption can only interfere with sound management of patients with allergy.

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PRESERVATION OF BLOOD IN PLASTIC BAGS

To the Editor:—The article by Ruesch and others in The Journal, April 2, page 1476, entitled "Continuing Hazard of Air Embolism During Pressure Transfusions," is an excellent discussion of this problem and ably presents an evaluation of the acceptable alternatives to the hazardous use of the air pump method. Unfortunately, in the comments concluding the article, the authors give an erroneous impression of the superiority of plastic bags. "Walters and co-workers [*Surg. Gynec. & Obst.*, Sept., 1957, p. 365] and Strumia and colleagues [*J. Lab. & Clin. Med.*, Aug., 1955, p. 225] stated that blood preserved in plastic bags shows less loss of platelets and longer red blood cell life than blood drawn in siliconized tubing and stored in siliconized bottles." Reference to the articles which are quoted in support of this statement reveals at once that both groups were comparing cell survival of blood collected in plastic bags with that of blood collected in standard glass bottles. Neither of them were using silicone treated (nonwettable) glass, nor did they mention the use of siliconized tubing.

Workers in the blood banking and blood transfusion services now generally agree that the improved cell survival observed when blood is collected in plastic bags is duplicated by the use of siliconized glass bottles. In addition there are definite disadvantages in the routine use of presently available plastic equipment, and several of these points are discussed in Dr. Ruesch's article. In view of the above comments it would hardly seem justifiable for the authors to urge that physicians "demand that their hospital blood banks and local Red Cross blood banks furnish blood in plastic containers."

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DANGER IN USE OF POTASSIUM PERMANGANATE

To the Editor:—I would like to call attention to the dangerous effects arising from the indiscriminate sale, across the counter, of potassium permanganate crystals and tablets. I am aware of several instances of severe ulcerations of the upper vagina resulting from the use of this drug by women who wished to produce an abortion. This chemical, when used undiluted in tablet or crystal form, is a potent escharotic. Three patients had large necrotic craters in the vagina. Bleeding from these ulcers can threaten life. Potassium permanganate, even for local use in a high dilution, is not an essential form of treatment today. I believe measures should be taken to prohibit its sale across the counters of the nation's drug stores, especially to persons without prescriptions.

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Sleepers

To the Editor:—Congratulations on the keen way The Journal is edited. Your gracious note of farewell to Saunders' front-cover ad is delightful and so well deserved.

This "sleeper" business, which you and Bill Dock so impishly enjoy, is tricky; suppose the unsleepy reader thinks you're a pair of dopes—and there is no public note of indignant correction? Do you plan to pull an Osler and write a leg-pulling letter to yourself? If so, sign such a letter Edgerton Yorrick Davis Jr., and a few real old-timers may get it!

Meanwhile, keep happy, laugh, and never be satisfied with the job you are doing.

All best.

Chauncey—*In Flight.*

ABSTRACTS FROM THE LITERATURE

INTERNAL MEDICINE

Coronary Heart Disease in Seven Racial Groups in Singapore. C. S. Muir. Brit. Heart J. 22:45-53 (Jan.) 1960 [London].

The author examined the pattern of coronary heart disease, as seen in the mortuary of the General Hospital in Singapore between 1948 and 1957, in 19,415 consecutive autopsies. Autopsy examination revealed that 558 of the 19,415 persons had died of coronary heart disease; 238 of them were Chinese, 244 were Indians from what is now India and Pakistan, 35 were Malays, 12 were Eurasians, and 29 were Europeans. Investigation proved that the Indian Moslems were twice as liable to die of coronary heart disease as were non-Moslem Indians (Hindus, Christians, Buddhists) and 20 times more liable than the Chinese or the Moslem Malays.

Examination of the protocols revealed the presence of a thrombus in the arteries of 242 of the 558 persons, whereas no thrombus was found in the remaining 316 persons. The average age of the thrombus-positive group at death among the non-Moslem Indians, Indian Moslems, and Malays was significantly lower than among the Chinese, whereas no significant difference in age was noticed among the non-Moslem Indians, Indian Moslems, and Malays. More non-Moslem Indians and Indian Moslems died of coronary occlusion in the 4th decade of life than did Chinese. Minor racial differences were noted in the thrombus-positive group, such as the low incidence of right coronary thrombosis in the non-Moslem Indians, as compared with the Chinese, and the generally more fulminating nature of the disease in the Indian Moslems. The coronary ostiums were involved in 6% of the 242 persons. Subintimal hemorrhage had occurred in 4%, while the thrombus was found on an ulcerated atheromatous plaque in 12%. Gross calcification of the arterial wall was present in 21%. There were no significant racial differences in this group.

The thrombus-negative group showed a remarkable similarity to the thrombus-positive group. The average age at death in the thrombus-negative group was also significantly lower among the non-Moslem Indians and Indian Moslems than among the Chinese, and there was no statistically significant difference between the Malays, non-Moslem Indians, and Indian Moslems. Myocardial necrosis was found in 140 of the hearts in this group. Rupture of the myocardium was noted in 4%, cardiac aneurysm in 2%, mural thrombus in 3%, and thromboembolic phenomena in 1%. There were no significant racial differences in this group.

Only 34% of the 19,415 autopsies were performed on female subjects. There were 16 women in the thrombus-positive group, 12 of whom were Chinese, and there were 25 women in the thrombus-negative group, 19 of whom were Chinese. Fifty-eight per cent of the Chinese women with thrombi had died before the age of 50 years, the peak incidence being in the 41 to 50 age group. In the thrombus-negative group 47% of the Chinese women had died before the age of 50 years, the peak incidence being in the 41 to 50 age group. Records, including prewar figures of the Registrar General in Singapore, show a fall in mortality from coronary heart disease during World War II, with a concomitant rise in deficiency diseases. This suggests that diet, as well as race, plays a part in the pathogenesis. Postwar records show that the incidence of coronary heart disease has been constantly rising in Singapore and neighboring Malaya.

Serum Glucose-6-Phosphate Dehydrogenase in the Diagnosis of Myocardial Infarction: Comparison of Its Clinical Value with that of Glutamic Oxalacetic Transaminase. W. Kerppola, E. A. Nikkilä, and E. Pitkänen. Acta med. scandinav. 166:17-24 (no. 1) 1960 (In English) [Stockholm].

While the elevation of the level of the serum glutamic oxalacetic transaminase (SGO-T) after acute myocardial infarction is a valuable index of myocardial necrosis, it has some drawbacks. It is not specific for myocardial infarction, and the elevated SGO-T level returns too rapidly to a normal level. A new approach was suggested to the authors by a study of triphosphopyridine-nucleotide-linked enzymes in various clinical disorders. It appeared that serum glucose-6-phosphate dehydrogenase (G6D) activity was increased after myocardial infarction, but was not affected by many other disorders, among them the hepatobiliary diseases. It was found that myocardial infarction causes an increase of serum G6D activity for 3 to 10 days after the onset of the disease.

To evaluate the clinical usefulness and limitations of this enzyme test, serial determinations of serum

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The place of publication of the periodical appears in brackets preceding each abstract.

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G6D and SGO-T activities were performed on 100 patients admitted to hospital for suspected cardiac infarct. In 60 cases the myocardial infarct was certain, or fairly certain, as judged on clinical grounds. In these the serum G6D and SGO-T tests were positive in 78 and 63% respectively. Most of the failures of the enzyme tests were due to late admission of the patient, and the superiority of the former test was due to the longer duration of elevated serum G6D than of SGO-T activity after the initial attack. Clearly false-negative G6D tests were indubitably present in 6 patients (10%) and corresponding SGO-T tests in 4 patients (7%). A nonspecific positive G6D and SGO-T test occurred in 3 and 8 cases respectively. The G6D activity is increased also after pulmonary infarction but remains normal in hepatobiliary disorders. The essential drawbacks of the G6D test are the lesser activity of this enzyme in serum and the often delayed response to cardiac infarction.

"Non-Cardiac" Congestive Heart Failure. D. A. Miller. J. Indiana M. A. 53:290-293 (Feb.) 1960 [Indianapolis].

Although venous circulatory congestion is most commonly due to cardiac failure, on occasions it may be due to noncardiac conditions. The recognition of this latter possibility is of more than academic interest, for unless it is differentiated from primary heart disease with failure, erroneous treatment will result. The author presents the histories of 3 patients to illustrate that cardiac failure of a normal heart is seen in 3 situations: (1) in high-output states; (2) in the presence of mechanical circulatory obstruction; and (3) in hypervolemic states. The 1st patient, a 58-year-old woman, was admitted to hospital for evaluation of painless swelling of the feet and legs. A roentgenogram of the chest revealed enlargement of the cardiac silhouette, and a hematological study revealed an anemia compatible with iron deficiency. Treatment with ferrous sulfate by mouth resulted in a rapid rise in reticulocyte count and hemoglobin value. On discharge, the heart was normal in size, and no murmurs were heard. There were no signs of venous congestion. A roentgenogram of the chest showed a marked decrease in the cardiac silhouette. The patient has been seen several times in the outpatient clinic and has had no further difficulties. The author points out that high-output states, such as anemia, hyperthyroidism, beriberi and A-V shunts, result in venous congestion because of the increased demand put on the heart by such disturbances.

When there is some mechanical circulatory obstruction, as in cardiac tamponade, constrictive pericarditis, amyloidosis, pure mitral stenosis, and subendocardial fibroelastosis, mechanical obstruction interferes with diastolic filling of the heart and with cardiac contraction, due to increased intracardiac pressure. The resultant impairment of inflow is followed by a rapid elevation of venous pressure. This is exemplified by the history of the 2nd patient, a man with inoperable bronchogenic carcinoma, who was cyanotic. Examination revealed dulness to percussion in the right anterior and lateral hemithorax, with absence of breath sounds in this area. Bilateral moist rales and rhonchi were noted. A roentgenogram of the chest showed a homogeneous density of the base of the right lung with marked enlargement of the cardiac silhouette. A diagnosis of pericardial effusion with tamponade, secondary to metastatic spread of bronchogenic carcinoma, was confirmed by pericardiocentesis. After a second pericardiocentesis and insertion of a polyethylene tube for continued drainage, there was no recurrence of cardiac symptoms, and congestive changes disappeared.

In hypervolemic states, such as glomerulonephritis, lower nephron nephrosis, and excess of fluid or steroid administration, venous congestion appears to be due to excessive sodium retention. The 3rd patient, whose history illustrates this condition, was a young woman with acute glomerulonephritis, who was hospitalized with shortness of breath, orthopnea, and swelling of the legs. Examination of the chest revealed rales, but no dulness. The heart and liver were enlarged. The roentgenogram of the chest revealed slight cardiomegaly, with congestive changes bilaterally and a pleural effusion on the right. The patient was given digitoxin which caused no apparent beneficial change in her condition. With sodium restriction and a high carbohydrate diet, however, she gradually became asymptomatic.

Some Practical Aspects of the Smoking-Cancer Problem. E. L. Wynder and D. Hoffmann. New England J. Med. 262:540-545 (March 17) 1960 [Boston].

The accepted principle in carcinogenesis—the greater the exposure to a carcinogen, the greater the risk of cancer—has also been established for tobacco smoke. Studies indicate that a reduction in the yield of smoke condensate of a cigarette and a reduction in the amount that comes in contact with the lung will be followed by a reduction in the risk of lung cancer. The authors determined the amount of smoke condensate of 10 leading American cigarette brands. They compared the quantity of smoke condensate collected from the first 30 mm. of an 85-mm. cigarette with the quantity from the second 30 mm. The ultraviolet fluorescence of inhaled and noninhaled cigarette smoke was studied to determine how much of the fluorescent material is absorbed by the lung on inhalation. To compare the benzo[a]pyrene content of the smoke condensate of 2 leading American nonfilter and filter cigarettes, chemical determinations of this, the most potent carcinogenic compound so far identified in tobacco-smoke condensate, were made.

The results of these studies suggested the following measures: moderation of smoking for those who cannot give up the habit; use of filter cigarettes with the lowest yield of smoke condensate; avoidance of smoking the cigarette to the butt, since there is significantly more smoke condensate in the latter part of the cigarette; and not inhaling deeply, since such a practice leads to much greater absorption of smoke condensate by the lungs. The benzo[a]pyrene content of various cigarette-smoke condensates proved to be similar when judged on a gram-for-gram basis. Per cigarette, however, it increases together with an increase in the amount of smoke condensate. Thus, the user of a cigarette with a high yield of smoke condensate will be exposed to more benzo[a]pyrene than one smoking a cigarette with a lower yield.

Three hundred four men, over 40 years of age, were interviewed regarding whether certain symptoms considered to be associated with heavy smoking, particularly chronic cough, disappeared or diminished when they changed from nonfilter to filter cigarettes. It appeared that filter cigarettes tend to diminish symptoms, especially that of cough.

Primary Aldosteronism, Observations on 2 Cases. F. Cortes, C. R. Shuman, and B. J. Channick. Am. J. M. Sc. 239:324-337 (March) 1960 [Philadelphia].

The authors report on 2 women, aged 43 and 48 years, with primary aldosteronism caused by an adenoma (aldosteronoma) of the left adrenal gland, who were admitted to the Temple University Hospital in Philadelphia during the past year. The clinical features of these 2 patients were entirely dissimilar and did not coincide with the syndrome described in many of the patients with primary aldosteronism reported on by other workers. The younger woman had been treated for hypertension for 5 years at another hospital. On admission she was in a state of peripheral circulatory collapse after an acute attack of diarrhea. Hypopotassemia, attributed initially to diarrhea, proved resistant to therapy with administration of potassium over a period of several weeks. The patient disclaimed any symptoms of weakness, paralysis, or tetany before her admission. The older woman was admitted for treatment of menometrorrhagia. She had been treated for hypertension and recurrent edema for 4 years. On 2 occasions the administration of diuretics had resulted in brief attacks of extreme muscular weakness. Retroperitoneal carbon dioxide insufflation revealed in both patients an enlargement of the left adrenal gland. Twenty-four-hour urine specimens showed elevated aldosterone levels (80 mcg. and 24 mcg., respectively), with normal 17-ketosteroid and 11-oxysteroid excretion.

Surgical removal of the left adrenal gland in both patients revealed almost identical adenomas. Large amounts of potassium salts were required to maintain normal serum levels of this electrolyte during the surgical intervention and the postoperative period. Postoperatively, the blood pressure dropped to shock levels in one patient and was restored to normal in the other. A transient period of hypertension was observed in both patients during the postoperative administration of cortisone. Both patients recovered, and abnormal glucose tolerance tests reverted to normal after recovery. The development of adrenal insufficiency 1½ years after the unilateral adrenalectomy in the younger woman was probably due to trauma from an unsuccessful attempt at a right kidney biopsy one year after the removal of the left adrenal gland. Replacement therapy successfully controlled this complication.

Tetany: Some Studies on the Tetanic Syndrome and Calcium Metabolism. B. A. Lamberg, R. Gordin, B. Kuhlbäck, and G. Björkenheim. Acta endocrinol. 33:317-346 (March) 1960 (In English) [Copenhagen].

The authors report on 196 patients in the Maria Hospital in Helsinki, who showed a vague disease picture characterized mainly by the presence of visceral pain of unknown causation, headache, and various symptoms pertaining to the autonomic nervous system. In an attempt to investigate the predisposition to tetany and certain aspects of calcium metabolism in these patients, a provocation test, i. e., Trousseau's or Trousseau-von Bonsdorff's test, was performed. The occurrence of typical carpal cramps was regarded as a sign of predisposition to tetany. The response to these tests was positive in 97 patients. Spontaneous attacks of tetany occurred in 38 patients. On the basis of the serum calcium level determined according to Kramer and Tisdall's method, 20 of the 97 patients were classified as having hypocalcemia and 77 as having a normocalcemic level. The latter group was further divided into the following subgroups: 7 patients with a history of thyroidectomy; 26 with a neurogenous condition, in whom the disease aspect was dominated by symptoms pertaining to the autonomic nervous system; and 42 with an idiopathic and 2 with a gastroenterogenous disorder. In addition, 18 patients with postoperative hypocalcemic hypoparathyroidism were investigated; in 16 of these patients the provocation test was positive, and in 2 it was negative, notwithstanding a low serum calcium level. Spontaneous attacks of tetany occurred in 10 of the 18 patients. Forty healthy persons served as controls, and all of them had negative results from the Trousseau-von Bonsdorff test.

The present study included the excretion of calcium and phosphorus in the urine, intravenous calcium tolerance tests, parathyroid hormone tolerance tests, and short-term treatment with a preparation of dihydrotachysterol (AT 10) for test purposes. The calcium excretion was less than 50 mg. in practically all the patients with hypoparathyroidism, but also in one of the control persons. In addition, an excretion of less than 50 mg. a day was observed in one patient with sprue and in one with idiopathic tetany. The responses to the intravenous calcium tolerance test showed a wide variation, and it was concluded that this test is inadequate as an ordinary clinical routine test. Two patients, one with postoperative hypoparathyroidism and the other with a normal serum calcium level and a history of thyroidectomy, had a pathological response to the parathyroid hormone tolerance test. In many patients dihydrotachysterol therapy brought about a rapid and marked increase in calciuria, an excretion of as much as 800 mg. a day being sometimes noted, although the changes in the blood were slight. This discrepancy in the response is emphasized, and checking of the excretion of calcium, in addition to checking of the blood calcium level, during dihydrotachysterol therapy is recommended.

In many patients the syndrome of tetany manifests itself only occasionally and under certain circumstances, but in others it may be grave enough to be called a disease. Patients with postoperative hypoparathyroidism constitute a separate group, in which the pathogenetic background seems to be clear. But it should be emphasized that there are also patients with postoperative hypoparathyroidism in whom no signs of a predisposition to tetany can be elicited even by provocation. Latent tetany often seems to be associated with a vague disease aspect. For the detection of a predisposition to tetany, the Trousseau-von Bonsdorff test is very valuable.

Pattern of Cholesterol Ester Fatty Acids in Serum in Normal Subjects and in Patients with Essential Hypercholesterolemia. P. Björntorp and B. Hood. Circulation Res. 8:319-323 (March) 1960 [New York].

Answers were sought to the following 2 questions: Is there any difference in the pattern of fatty acids in patients with essential hypercholesterolemia as compared with normal persons? Is the pattern of fatty acids changed by the substitution of corn oil or corn oil plus pyridoxine for other fats in the diet? Twelve patients with essential hypercholesterolemia were investigated. Seven were members of families with essential hypercholesterolemia and xanthomatosis. All the patients had cholesterol values exceeding 325 mg. per 100 cc. in repeated determinations. Six presented xanthomas. All showed a clear serum in the fasting state and had a normal uptake of iodine and no signs of biliary obstruction or kidney disease of the nephrotic type. For comparison, 10 normal subjects were matched as regards age and sex with the 10 patients studied on ad libitum diet. In 3 patients the analyses were repeated after the substitution of corn oil for other fats in the diet, and 2 of them were analyzed after the addition of pyridoxine to the corn oil regimen. One patient was followed 18 months.

Patients with essential hypercholesterolemia had an absolute increase in the amount, but generally a lower percentage content of dienes in their cholesterol esters than had normal subjects. After the change to corn oil, the content of polyunsaturated fatty acids increased to levels sometimes considerably above those in the normal subjects, although the total serum cholesterol in one of these patients was by no means normalized. The addition of 100 mg. of pyridoxine to the corn oil regimen did not produce any further decrease in the serum cholesterol level and did not produce any changes in the fatty acid fractions. The absolute increase in the amount of polyunsaturated fatty acids in the cholesterol esters in patients with essential hypercholesterolemia, particularly after an extremely high intake of unsaturated fat, speaks against an inhibition in esterification by polyenes as being of central importance.

Mimetic Features of Rheumatic-Fever Recurrences. A. R. Feinstein and M. Spagnuolo. New England J. Med. 262:533-540 (March 17) 1960 [Boston].

The authors report on 161 patients who had had more than one attack of rheumatic fever and who had been examined at the Irvington House rheumatic fever prophylaxis clinic in Irvington-on-Hudson, N. Y., during at least the most recent attack between 1956 and 1959. These patients had a total of 370 attacks, each of which fulfilled the modified Jones criteria, which define acute carditis according to 4 possible manifestations, namely, murmurs of valvular involvement, cardiac enlargement, pericarditis, or congestive heart failure. Valvular involvement in each attack was defined by the presence of a diastolic murmur at the base or left sternal border or a long systolic murmur loudest at the apex and radiating to the axilla, with or without an associated apical diastolic murmur. Sixty-one patients had no valvular involvement with their 1st attack, and none with subsequent attacks. They have remained free of heart disease. Ninety patients had valvular involvement with their very 1st attack. Their subsequent attacks brought either no change in the valvular involvement or new valvular involvement, and some of these patients had increased cardiac enlargement, pericarditis, or congestive heart failure. In the remaining 10 patients no valvular involvement was found at the 1st attack, but a diastolic murmur was discovered at a subsequent attack. In at least 8 of these patients, the pattern of this discovery suggested that the murmur might have been present without being recognized at the 1st attack. In all these 10 patients, the resultant heart disease, despite recurrent attacks, was relatively benign. Noncardiac manifestations of rheumatic fever were frequently repetitive in all the patients, and the features of one attack mimicked those of previous attacks particularly often in patients without valvular involvement.

These results suggest that the rheumatic host has a specific and persistent susceptibility to get or to avoid valvular involvement. If it does not occur with the 1st attack, it does not occur (with dubious exceptions) in subsequent attacks. In most patients in whom rheumatic heart disease develops, the valvular involvement is manifested in the very 1st attack. Subsequent attacks in this group are particularly dangerous because they may lead to further cardiac damage. In addition to their biological implications, these data are pertinent to the clinical problem of selecting rheumatic patients for continuous and indefinite antistreptococcic prophylaxis. While patients who have had rheumatic fever and who have had valvular involvement should be given antistreptococcic agents continuously and indefinitely, those without valvular involvement might not need continuous prophylaxis to be continued indefinitely. It could be maintained after a rheumatic attack for the first few years during which the patient is most susceptible to recurrences. At some arbitrary time, such as 5 years after an attack, or some arbitrary age, such as 18 years, the continuous prophylaxis might be stopped, after careful auscultatory confirmation of the cardiac status, in those patients with no valvulitis. Thereafter, the prevention of rheumatic recurrences would be attempted by prompt recognition and treatment of recognizable streptococcic infections when they occurred.

SURGERY

Late Results of Duodenorrhaphy: A Roentgenologic Study on 300 Patients with Ulcer of the Superior Portion of the Duodenum Who Had Undergone Duodenorrhaphy. L. Pace. Riforma med. 74:16-20 (Jan. 2) 1960 (In Italian) [Naples].

A roentgenologic follow-up study was made on 300 male patients, aged between 17 and 55 years, who had undergone duodenorrhaphy for ulcer of the superior portion of the duodenum. This study was carried out within the 1st postoperative year in half of the patients and within 4 postoperative years in the remainder. The roentgenologic findings indicate that duodenorrhaphy has been only a temporary measure for the treatment of the ulcerous disease, and that inevitable anatomic and functional changes take place in the affected portion of the duodenum after the operation. Persistent functional changes of the involved portion of the duodenum were observed in 60 patients. Deformities of the contour of the involved duodenum were observed in 160 patients, 20 of whom had the extreme picture of stenosis of the pylorus. The shadow of the niche persisted in the remaining 80 patients who, together with the preceding 20 patients, proved to have a persistent ulcer on 2nd operation.

The Effect of a Tissue Committee on Appendectomy in a General Hospital. H. R. Sharpe Jr. Wisconsin M. J. 59:135-138 (Feb.) 1960 [Madison].

A tissue committee was established in 1954 at the 350-bed general community hospital in Fond du Lac, Wis. The committee reviewed all surgical cases in which the preoperative diagnosis and the pathological report differed. It was found that most of the cases reviewed were appendectomies, and so all cases of appendectomy were reviewed. Ten surgeons had performed the appendectomies. In 1954 a total of 178 patients were operated on for appendicitis, and in 1957 the total was 79 patients; this represents a drop of 56% in appendectomy rates in a 3-year period. All specimens were studied in cross section at the proximal and distal ends and also in the middle third. Acute suppurative appendicitis fulfilled the pathological findings of acute inflammation. Chronic recurrent appendicitis showed perivascular round-cell infiltration in the serosa. A few appendixes showed fibrous cords with fibrous replacement of the appendix and lumen; these were called fibrous appendixes. The remaining appendixes showed no change and were called noninflammatory appendixes (NIA).

Of the 178 patients operated on for appendicitis in 1954, there were 127 in whom acute appendicitis was suspected. The pathological studies in these 127 patients revealed acute appendicitis in 72, recurrent appendicitis in 9, and NIA in 46. Of the 79 patients operated on in 1957, there were 62 in whom acute appendicitis was suspected. The pathological diagnoses in these 62 patients were acute appendicitis in 50, recurrent appendicitis in 2, and NIA in 10. The author believes that the reduction in the number of patients with acute appendicitis from 72 in 1954 to 50 in 1957 was partly due to the building of a community hospital in a nearby area, the population of which had been previously served by the hospital under consideration here.

With regard to chronic recurrent appendicitis, the author says that in the 1954 series 51 patients were operated on for chronic recurrent appendicitis, and in the 1957 series 15. Of the 51 patients in 1954, 43 were reported as having NIA, 4 chronic recurrent appendicitis, and 4 fibrous appendix. Of the 15 in 1957, 14 were reported as having NIA, and 1 acute suppurative appendicitis. At the outset of the tissue committee's scrutiny, the cry of possible increased mortality due to perforating appendicitis from increased caution on the part of the surgeon and the referring physician was raised. Statistics proved that these fears were groundless. All 16 patients with ruptured appendix were operated on promptly after being given a preoperative diagnosis of acute appendicitis. The only exception was a patient who was operated on for acute intestinal obstruction 6½ hours after admission. She was a 75-year-old woman with abdominal pain, vomiting, and abdominal distention of 5 days' duration. At laparotomy a far-advanced peritonitis was present, and the patient died.

Methods of improving the accuracy of the diagnosis of acute appendicitis are discussed. Elevation in the white blood cell count still is an important aid in the diagnosis of acute appendicitis; it was found in 96% of the patients. Observation of a patient with suspected appendicitis is a safe and recommended procedure. Practically all the patients operated on with the diagnosis of chronic appendicitis had normal tissue removed. Chronic appendicitis is not a surgical disease.

Acute Renal Failure: Eighty Cases of Renal Tubular Necrosis. J. E. Kiley, S. R. Powers Jr., and R. T. Beebe. New England J. Med. 262:481-486 (March 10) 1960 [Boston].

The authors report observations on 80 patients with acute renal tubular necrosis, 48 of whom were treated by hemodialysis. The Kolff rotating-drum artificial kidney was used. Hemodialysis was performed when clinical deterioration, as evidenced by impaired cerebration, acidosis, or pulmonary congestion, indicated that the patient was likely to die unless dialyzed. Although hemodialysis usually resulted in improvement, it was more effective in the prevention of clinical deterioration than in restoring the patient after severe deterioration had occurred.

The cases were of 6 different groups: 1. The nephrotoxic group included 9 patients who had acute tubular necrosis from mushroom poisoning, sulfonamide reaction, and exposure to carbon tetrachloride, diethylene glycol, and bichloride of mercury. Seven patients received dialysis. Two patients died, one in the dialyzed and the other in the undialyzed group, both of pneumonia. 2. In 4 patients renal shutdown was associated with a transfusion reaction, but there was no severe disease affecting other systems. All 4 patients survived, 2 having been treated by dialysis. 3. In 10 patients the acute renal insufficiency followed hemorrhage at the time of delivery. In 5 of these cases, toxemia was a complicating factor. The group was equally divided between dialyzed and undialyzed patients, with the dialyzed patients all showing relatively protracted oliguria. All 10 patients survived. 4. The 28 patients of the postoperative group, in whom oliguria developed after such operations as prostatectomy, cholecystectomy, gastrectomy, nephrectomy, hysterectomy, salpingectomy, pneumonectomy, osteotomy, and pelvic exenteration, differed from those previously enumerated because of the presence of serious disease in addition to the renal lesion. Eighteen of the 28 patients required dialysis, and these had a relatively longer period of oliguria and a mortality of almost 70% in contrast to one of 50% in the undialyzed group. 5. Of the 17 patients in whom acute renal failure developed as the result of injuries suffered in an accident, 12 required dialysis, and here again the dialyzed group was characterized by more protracted oliguria and a higher mortality. 6. This last group included 12 patients in whom acute renal failure followed surgery on the aorta, either the elective removal of aneurysms or the emergency treatment of ruptured or dissecting aneurysms. Death resulted in all but one of these patients, generally from generalized atherosclerosis. Half of these patients received dialysis, but none survived the period of oliguria.

The authors combine the 6 groups of patients into 2 groups, one composed of the nephrotoxic, hemolytic, and postpartum cases and the other of the postoperative, post-traumatic, and postaortic surgery cases. The former group was characterized by severe renal disease not associated with other serious lesions, and the latter by severe renal disease in association with other serious lesions. The mortality of the former group was 8.7%, and that of the latter 65%. It is difficult to separate the undesirable effects of dialysis from the effects of the disease being treated, but the authors feel that dialysis caused death in 4 patients.

Primary Carcinoma of the Gall Bladder: Presentation of Seventy Cases from the Rhode Island Hospital and a Cumulative Review of the Last Ten Years of the American Literature. G. O. Strauch. Surgery 47:368-383 (March) 1960 [St. Louis].

Observations on 70 patients with primary carcinoma of the gallbladder, treated at the Rhode Island Hospital, in Providence, from 1948 to 1958, are presented, and the 482 cases reported in the American literature during the past 10 years are reviewed. The 482 cases were discovered among a total of 34,242 biliary tract operations, an incidence of 1.41%. Like other diseases of the gallbladder, carcinoma is most frequent in women; in the collected series more than 75% of the patients were women.

The incidence of gallstones in gallbladder carcinoma has ranged in various reports from below

50 to 100%; in the patients studied by the author, it was 54.3%. The real controversy concerning cholelithiasis and carcinoma lies in the possible etiological relation between the two. It has been suggested that gallstones may cause carcinoma. In addition to the association, many authors cite the relation between bile salts, cholesterol, and known carcinogenic agents in the chemical make-up of gallstones. Other possible etiological factors in gallbladder carcinoma are infection (in the form of cholecystitis), benign neoplasms (such as papillomas and adenomas), and exogenous factors. With regard to this last point, the author directs attention to experimental studies on dogs in which carcinoma of the gallbladder and biliary tree developed after chronic feeding of large doses of an insecticide.

In its early, potentially curable stage, carcinoma of the gallbladder is largely asymptomatic, or the symptoms are those of associated benign disease. It is only when the malignancy has spread beyond the confines of the gallbladder that it produces severe symptoms, which are relentless and progressive and lead to death within a few months. It is then that obstructive jaundice may appear, accompanied by pain of a severe, steady, gnawing quality. A careful history may uncover anorexia, weakness, malaise, and weight loss over a short interval. Physical examination frequently reveals a hard right upper quadrant mass, or, less commonly, an enlarged liver. Ascites may be present. In other patients there may be ill-defined abdominal pain, discomfort and vague gastrointestinal symptoms, and anorexia. Laboratory studies are of little help in the diagnosis.

If a definite diagnosis can be established clinically or by liver biopsy, operation is contraindicated unless complicating factors, such as jaundice, perforation, or intestinal obstruction, are the indications. This opinion is shared by many investigators because of the proved incurability, the high operative mortality, and the uniform lack of palliation. The author knows of only one cure obtained, in the past 10 years, by radical resection in carcinoma grossly extending beyond the gallbladder. In the absence of effective surgical treatment for all but the earliest lesions, the best hope for reducing the mortality from this disease lies in earlier cholecystectomy in patients with benign gallbladder disease.

Antrectomy with Vagectomy or Partial Gastrectomy with or without Vagectomy for Chronic Duodenal Ulcer: A Comparative Analysis. L. T. Palumbo, W. S. Sharpe, D. J. Lulu, and others. Ann. Surg. 151:367-373 (March) 1960 [Philadelphia].

This report presents the comparative results of antrectomy-vagectomy with those of partial gastrectomy with or without vagectomy in a total of 346 male patients. Antrectomy-vagectomy was performed on 115 patients, partial gastrectomy on 189, and partial gastrectomy with bilateral vagus resection on 42. Antrectomy-vagectomy has given better results than the other 2 procedures; all the patients in the antrectomy-vagectomy series and approximately two-fifths of the remainder gained weight. The dumping syndrome was milder and less frequent in those undergoing antrectomy-vagectomy than in the remaining 2 groups. Diarrhea did not occur after a period of readjustment in the antrectomy-vagectomy series, but it was a recurring problem in the other 2 groups. Antrectomy with vagectomy seems to be superior to the other 2 procedures for the following reasons: lower morbidity and mortality rate; more rapid rehabilitation; less side-effects; easier operative performance; reduction of the operating time to one-half of that required for either of the other 2 procedures; shorter hospital stay; and least chance for recurrent or marginal ulcer formation.

Intestinal Angina and Infarction. A. A. Klass. Canad. M. A. J. 82:620-623 (March 19) 1960 [Toronto].

In 1950 the author operated on a patient with acute complete occlusion of the superior mesenteric artery. This presented him with a choice of either resecting the intestine from the ligament of Treitz to the midtransverse colon or simply closing the abdomen. He rejected both and instead dissected out the origin of the superior mesenteric artery, opened it, and removed the obstruction. He repeated this procedure on another patient a year later. The 1st patient died of acute heart failure due to coronary occlusion, and the 2nd of intraperitoneal hemorrhage resulting from an excessive response to heparin. In both cases, however, postmortem study revealed that the superior mesenteric vascular channels were patent and that the intestine in each case was viable. Thus, it was established that the surgical treatment of mesenteric vascular occlusion ought primarily to be directed toward the artery rather than toward the intestine. Since then there have been reports of cases in which removal of obstruction from the origin of the superior mesenteric artery proved successful.

The condition is another form of "effort" angina, which includes angina pectoris, intermittent claudication, and intestinal angina due to mesenteric ischemia. There may be some quarrel with the term "intestinal angina." The triad of abdominal pain, weight loss, and disturbance of intestinal rhythm may be mistaken for occult gastrointestinal malignancy or chronic pancreatitis. When exploratory laparotomy does not support either of these diagnoses, the malabsorption syndrome may be thought of, but the author feels that this last diagnosis, or irritable colon, may actually be caused by incomplete mesenteric occlusion.

Conservative treatment ought to relieve those patients with moderate degrees of ischemia. Since both motility and absorptive capacity are taxed by large meals, the indication is for light meals at frequent intervals. Antispasmodic drugs and small repeated doses of codeine or opium tincture will delay the rush of intestinal contents. Before surgical exploration is undertaken with a view to thromboendarterectomy of the superior mesenteric artery or to some bypass procedure, the following 3 criteria must be satisfied: 1. The "total" patient must have been evaluated. 2. The combination of abdominal pain and weight loss must be sufficiently compelling to justify an "exploratory laparotomy," irrespective of the possibility of intestinal angina. 3. The patient should have other evidence of atherosclerosis or be in the age group in which this disease is a possibility.

Bronchogenic Carcinoma: Comparison of Natural Course and Treatment with Resection, X-radiation, and Nitrogen Mustard. F. A. Hughes Jr., J. W. Pate, and R. E. Campbell. J. Thoracic & Cardiovas. Surg. 39:409-416 (March) 1960 [St. Louis].

The authors analyze data on 547 consecutive proved cases of bronchogenic carcinoma. The patients were followed for from 6 months to 12 years at the Veterans Administration Medical Teaching Group Hospital, Memphis, Tenn. The median age of the patients was 58 years. More than 60% of the patients experienced symptoms more than 3 months before hospitalization. The average duration of symptoms before hospitalization was over 8 months, and 16% of the patients had symptoms more than 2 years before being admitted. Seven per cent of the patients had abnormal chest roentgenograms in the absence of symptoms; in 65% of the patients a mass was demonstrated on roentgenograms of the chest. The diagnosis was proved by surgery in 38%, by bronchoscopy in 29%, at autopsy in 20%, and by supraclavicular node dissection in 13%. Supraclavicular node dissections were done on more than 100 patients, but gave histological proof of cancer in only 20% of these cases. When there were no palpable nodes, the procedure was of little help in making the diagnosis. Cytological examination of the sputum was disappointing as a diagnostic aid during its few years of use, but in the last 2 years its accuracy was over 80%. The differentiation of a metastatic cancer from primary bronchogenic carcinoma was difficult in some cases.

The operability rate was 41.4% of all the patients admitted; the resectability rate was 60.3% of the patients operated on. Lobectomy in properly selected cases gave results comparable to pneumonectomy. The operating room mortality was less than 1%, and the 30-day mortality was slightly over 2%. The 5-year survival rate after resection was 37%. High-voltage irradiation and nitrogen mustard therapy proved valuable in prolonging useful life and in palliation. The 5-year survival rate of all patients with bronchogenic carcinoma, originally admitted to this hospital, was 11.5%.

Nonfunctioning Carcinoma of the Adrenal Cortex. C. D. Knight, B. E. Trichel, and W. R. Mathews. Ann. Surg. 151:349-358 (March) 1960 [Philadelphia].

The authors report on 3 men and 4 women, aged between 42 and 76 years, with nonfunctioning carcinoma of the adrenal cortex. Four patients complained of pain in the left upper abdominal quadrant, and one complained of an abdominal mass. Three patients had a palpable mass in the abdomen, which had been undetected by the patient. The complaints of one patient were related to a metastatic lesion. Weight loss was not a frequent symptom, and the average hemoglobin level was 10.7 Gm. per 100 cc. These were late symptoms, and review of the records yielded no early symptoms which might have led to earlier diagnosis.

The diagnosis is usually suggested by pyelography, either intravenous or retrograde. Five patients showed pyelographic abnormality consistent with the diagnosis. Surgical exploration usually is necessary to establish the exact etiology of the tumor. Capsular invasion and distant metastases are the most reliable criteria of malignancy. The only successful treatment for this tumor is surgical excision. Abdominal approach was utilized in 3 patients, and flank (kidney) incision in 4. One patient died 7 days after the operation. One patient is alive and well 9 years after the operation, and another is alive 16 months after an exploratory operation, although the tumor was not removed. The postoperative survival periods of 3 patients were 2, 12, and 34 months respectively. One patient has received teletherapy with radiocobalt (Co^{60}), and although she is living after 16 months, a palpable tumor remains.

Calcific Mitral Stenosis and Mitral Valvotomy. G. Michell. Brit. M. J. 1:687-691 (March 5) 1960 [London].

This report is concerned with the efficacy of mitral valvotomy in patients with mitral valve calcification, 109 patients having been subjected to valvotomy from 1954 to 1958. Eight were excluded from the study, either because aortic or tricuspid valvotomy was performed simultaneously with the mitral valvotomy or because of severe aortic incompetence. There were 22 men and 79 women whose cases were analyzed, and all had dominant mitral stenosis. Calcium was found on the mitral valve in 32 patients, of whom 10 were men and 22 women. The deposits were moderate or heavy in 7 of the 10 men, but in only 8 of the 22 women.

About half of the patients with significant calcium deposits had associated mitral incompetence. No evidence of incompetence was found at operation in 81 patients, but in 28 of these a jet of incompetence developed after valvotomy.

Instrumental dilatation of the mitral valve was used in patients on whom valvotomy could not be obtained digitally. An adequate valvotomy was possible in practically every case, especially with the use of the transventricular dilator, even in patients with calcified valves. Instrumental dilatation may cause mitral incompetence more often than will digital dilatation. The incidence of postoperative mitral incompetence did not appear to be significantly greater in patients whose valves were calcified than it did in the noncalcified group. If incompetence is present preoperatively, the risk of worsening the incompetence seems no greater in patients with valvular calcium. Results of surgery are generally poor in combined mitral stenosis and incompetence, and do not correlate with the presence or absence of calcium or the size of the valvotomy. The functional effects of minimal incompetence after mitral valve surgery have not been adequately studied. An adequately dilated, yet slightly incompetent, valve would seem to be preferable to one which is competent, yet insufficiently split.

Surgical Treatment of Regional Enteritis. B. P. Colcock and J. H. Vansant. New England J. Med. 262:435-439 (March 3) 1960 [Boston].

The authors report on 158 male and 146 female patients with regional enteritis, who were operated on at the Lahey Clinic in Boston between 1933 and 1958. Chronic partial obstruction of the small intestine was the most frequent indication for surgical intervention with an occurrence in 254 (83.6%) of the 304 patients. Abdominal mass, external fistula, and internal fistula were the indications in 51 (16.8%), 52 (17.1%), and 55 (18.1%) respectively. Gross rectal bleeding was present in 27 patients (8.9%), acute perforation in 9 (2.9%), and acute abdominal pain in 8 (2.6%). In 277 patients (91.1%) there were 346 resections of the involved organs, including 293 resections of the terminal ileum and ascending colon, 42 resections of the small intestine, 10 combined resections of a proximal skip area in addition to the terminal ileum and ascending colon, and 1 gastric resection for recurrent regional enteritis involving the stomach. The mortality rate after these 346 resections was 1.73%. Of the patients treated by one or more resections, 76.3% had no evidence of recurrent regional enteritis; 52.2% of these patients had been followed up for longer than 5 years since the date of the last operation.

The reported data indicate that radical extirpation of the organs involved in regional enteritis offers a good chance for recovery, with a minimal operative risk. Even patients who require a 2nd or a 3rd resection have a better than 50% chance of remaining well. Resection is considered to be the surgical treatment of choice in the management of regional enteritis.

Mediastinal Teratoma in Infancy: Report of Successful Removal from Premature Infant and Review of Literature. R. H. Adler, S. A. Taheri, and D. H. Weintraub. J. Thoracic & Cardiovas. Surg. 39:394-404 (March) 1960 [St. Louis].

Observations on a large mediastinal teratoma, which the authors recently removed from a 2-day-old, prematurely born infant, stimulated their interest in such teratomas in infants. The child was delivered during the 7th month of gestation following spontaneous rupture of the membranes. The obstetrician noticed costal retraction. The infant's color was dusky. Moderate respiratory distress continued with xiphoid retraction and transient episodes of cyanosis. Breath sounds were diminished. The possibilities of atelectasis or hyaline membrane disease were entertained. On the 2nd day the left hemithorax was dull to percussion. Roentgenoscopy of the chest showed a large homogeneous mass, which occupied most of the left hemithorax and displaced the mediastinum to the right. Operation was performed on the basis of a diagnosis of mediastinal tumor or cyst.

An encapsulated dark, red, solid mass, which practically filled the entire left hemithorax, presented. It was necessary to divide the 5th rib to expose the base of this mass. A number of large vessels entering the tumor from the mediastinum were divided. A 1-cm. adherent piece of pericardium was removed with the tumor. A paralyzed left diaphragm (acquired eventration) was repaired several weeks after the teratoma had been removed by using a reinforcing patch of knitted Dacron mesh. Dyspnea disappeared after the repair of the elevated diaphragm.

Reviewing the literature, the authors found reports of 26 infants with extrapericardial teratomas. Practically all mediastinal teratomas in infancy caused signs and symptoms, or else they were discovered at postmortem examination. Cough, dyspnea, and cyanotic episodes are the predominant symptoms in infants. With large tumors filling the hemithorax, the involved side may lag with respiration and show protruding intercostal spaces. The percussion note will be flat with diminished breath sounds, and the displaced maximum cardiac impulse may reflect a mediastinal shift. A roentgenogram of the chest will usually show a dense, rounded mass with sharply defined borders projecting laterally into either hemithorax and blending centrally with a mediastinal cardiac shadow. Unless the tumor is intimately adherent to the heart or aorta, as with intrapericardial teratomas, the mass is frequently well circumscribed and easily shelled out from its surroundings at operation.

Islet Cell Tumors of the Pancreas and Hyperinsulinism. F. A. Rogers. Am. J. Surg. 99:268-282 (March) 1960 [New York].

The author reports on 17 patients with hyperinsulinism attributed to functioning islet-cell tumors, who were observed at the Los Angeles County General Hospital in the past 25 years. During the same period 10 other nonfunctioning islet-cell tumors were found. Fourteen patients with functioning tumors were operated on, while in 3 the tumors were identified at autopsy. Seven patients had an adenocarcinoma, and 6 of them had gross metastases. Three of the 14 patients undergoing surgery died in the early postoperative period; 2 had an adenocarcinoma. In the group with operable disease, 7 survived surgery for excision of a single adenoma and were cured within follow-up periods of 3 to 14 years. Five other patients had gross metastases, and only biopsy was performed.

The 2 remaining patients underwent exploration, and no tumor was found. In one patient, a 40-year-old woman, autopsy revealed multiple small adenomas in the body and tail of the pancreas, along with diffuse hypertrophy of all islet tissues and a single small nodule classified as an adenocarcinoma. In the other patient, a 23-year-old man, surgeons failed to find a 2.5-cm. adenoma on the inferior border of the body of the pancreas. The patient underwent exploration twice in 1942. He died after repeated convulsions 20 months later. The main postoperative complication was transient diabetes lasting from 1 to 10 days after the operation.

A Follow-up Study of Aortoiliac Reconstruction. R. C. Shepherd and R. Warren. Surg. Gynec. & Obst. 110:346-352 (March) 1960 [Chicago].

The authors report on 45 men and 7 women, between the ages of 32 and 70 years, who underwent surgical reconstruction for aortoiliac obliterative arteriosclerosis at the Peter Bent Brigham and the West Roxbury Veterans Administration hospitals, in Boston, between 1952 and 1958. The commonest symptom was intermittent claudication which occurred in 48 of the 52 patients. The duration of symptoms varied from 9 days to 15 years. Thromboendarterectomy was performed on 19 patients, and grafting, with or without thromboendarterectomy, on 33. There were 8 deaths, an operative mortality of 15.4%. In 40 (77%) of the 52 patients operated on, the reconstructions were patent at the time of discharge from the hospital. This figure represents 90% of the 44 patients discharged alive. The late closure rate for the patients leaving the hospital with patent segments, and being followed up for at least a year, was 35.5%, most closures taking place in the 1st year. In only one patient with late closure did gangrene occur.

In 10 of the 21 patients who had coincident femoropopliteal occlusions, only the aortoiliac element of the disease was treated. In only 3 of them was symptomatic improvement noted, and 2 of the 3 had later closures of the reconstructed segment. In the remaining 11 patients grafts were inserted between the aorta and the iliac artery above and the popliteal below. All the 9 survivors but 1, who had an associated posterior tibial block, became asymptomatic. One patient, whose reconstruction closed after 21 months, successfully underwent reoperation with a similar graft, and in 6 patients (55%) the grafts have now remained open for more than a year. A more radical approach to reconstruction is recommended for arteriosclerosis obliterans involving the aortoiliac segment than is recommended for that involving the femoral segment alone.

Diagnosis and Results of Treatment in Gastric Polyps. E. G. Huppler, J. T. Priestley, C. G. Morlock, and R. P. Gage. Surg. Gynec. & Obst. 110:309-313 (March) 1960 [Chicago].

The authors report on 465 patients in whom the clinical diagnosis of gastric polyp was made at the Mayo Clinic between 1925 and 1951. Of these patients, 165 were not operated on, and 300 were treated surgically. Of those on whom an operation was performed, a diagnosis of adenomatous gastric polyp was confirmed by the surgeon in 206, while in 94 the clinical diagnosis of adenomatous gastric polyp proved to be an error. Of the 206 patients, 181 proved to have benign adenomatous lesions on microscopic examination of the operative specimen, and 25 had adenomatous polyps with zones of adenocarcinoma, graded 1 or 2, at the tip without invasion of the stalk. The 94 patients had a variety of lesions other than adenomatous polyps, including polypoid carcinoma, malignant lesions of different types, and various other benign gastric lesions. In the combined group of 300 patients operated on, about 60% had benign gastric polyps, 20% had other benign lesions, and 20% had malignant lesions.

Roentgenologic examination after the ingestion of barium was the most frequently employed diagnostic procedure. In an attempt to evaluate the accuracy of the roentgenologic diagnosis, the surgical and pathological findings were considered in 227 patients in whom the roentgenologist made the preoperative diagnosis of "gastric polyp or polyps" with no qualifying remarks regarding possible cancer or other types of lesions. When a single gastric polyp was diagnosed by the roentgenologist, a single lesion of some type was found by the surgeon in 82% of the patients. When the roentgenologic diagnosis was multiple polyps, multiple lesions of some type were found in 79% of such patients. Roentgenologic examination is the most accurate diagnostic procedure, but it is less accurate in gastric polyps than in most gastric lesions.

A follow-up study of 5 years or more after operation was made on all 300 patients. A total of 92% of the patients who had benign gastric polyps removed were alive 5 or more years later. This is equivalent to the survival rate of the "normal" population of the same age and sex distribution. The survival rate was 78% for those who had polyps removed which showed malignant changes in the tip.

The Surgical Considerations of 258 Patients with Carotid Artery Occlusion. E. S. Gurdjian, W. G. Hardy, and D. W. Lindner. Surg. Gynec. & Obst. 110:327-338 (March) 1960 [Chicago].

The authors report on 180 men and 78 women with occlusion of the carotid artery in the neck, proved either by angiography or by surgical exploration, who were examined at the Grace and Detroit Memorial Hospitals, in Detroit, between 1948 and 1959. Of the 258 patients, 193 were between the ages of 51 and 70 years, 29 were less than 50, and 36 were over 70. Complete occlusion of the internal carotid artery was observed in 131 patients; in 53 of these, the occlusion occurred on the right side; in 69, on the left side; and in 9, bilaterally. Partial occlusion of the internal carotid artery was observed in 127 patients, with right-sided involvement in 46, left-sided involvement in 34, and bilateral stenotic lesions in 47. Initial unconsciousness in the apoplectic form of onset of the disease was noted in 28 patients. Nineteen patients had convulsions, and among the minor complaints in 52 patients were recurrent attacks of dizziness or momentary syncope, usually not associated with falling. Hemiplegia or hemiparesis was noted in 131 patients.

Of the 131 patients with complete occlusion of the internal carotid artery, 83 were operated on, and 48 underwent angiography only. Surgical treatment in the 83 patients consisted of excision of a portion of the artery, intimectomy, exploration, thrombectomy, and/or sympathectomy. Those patients who had surgical intervention fared somewhat better (64% were working and walking) than those who refused operation or were in a dying state and, therefore, were not operated on (52% working and walking). In the group of 127 patients with partial occlusion, 25 were operated on for relief of stenosis, 22 had intimectomy, and 1 had the scar from a post-thyroidectomy removed to repair the deforming stenosis of the carotid bifurcation. In one patient, the external carotid artery was anastomosed with the internal carotid artery, bypassing the stenosis; in another the artery was ligated.

Carotid artery occlusion in the neck cannot cause a stroke, unless the collateral supply of blood at the base through the carotid and the 2 vertebral arteries is deficient, or there has been a forward embolism from the atheromatous disease with implication of the small vessels of the brain resulting in varying degrees of disability, or there is a congenitally anomalous circle of Willis. In other cases in which there is an atheromatous lesion, a period of lowered level of blood pressure may be further intensified by the presence of stenosis, resulting in ischemia in the distribution of the vessels. This may be an important factor if one were to assume that atheromatous lesions, occurring in the secondary and tertiary branches of the main stenotic vessels, cause the blood pressure to be precipitously lower in the region of their distribution. Early angiographic studies to detect the presence of stenosis of one or the other carotid artery may allow repair before dangerous end-results occur.

It is difficult, with the amount of information available, to say how much good is accomplished by the more normal reestablishment of blood flow through a given carotid artery by surgical intervention. Although in many cases the results may not be significant for the proximate future, they may be important for the distant future when one or the other of the vessels on the other side may be similarly involved. Prognosis in carotid artery disease, obviously, should be very guarded. Results frequently depend on factors other than removal of an atheroma in a given region of the vessel, the most important being the collateral supply at the base of the brain and the condition of the other 3 vessels in the neck.

Considerations in 97 Palliative Operations on Patients with Tumor of the Head of the Pancreas. E. Pizzecco. Chir. ital. 11:634-650 (Oct.) 1959 (In Italian) [Milan, Italy].

Ninety-seven patients with tumor of the head of the pancreas underwent palliative operations designed to restore the biliary passage. The mortality rate after the operation was higher the older the patients were and the longer the period between the onset of the neoplastic disease and the operation. The most frequent causes of postoperative deaths were hepatorenal insufficiency and hemorrhage. Hepatorenal insufficiency took place within a week after the operation, and hemorrhage occurred later. Itching and pain subsided after the operation to a greater extent and more rapidly than did jaundice. Patients regained weight after the operation but only slightly and transitorily. There were frequent operative complications in this series. However, mortality risk among patients undergoing palliative operation was only slightly lower (26.8%) than that among those undergoing radical operation. Even so the survival rate was not impressive (5.8 months). Although radical operation has a slightly higher operative risk, it provides a better chance of survival than does the palliative one, which should be undertaken as early as possible.

NEUROLOGY & PSYCHIATRY

Epilepsy in the Families of Epileptics. V. Eisner and S. Livingstone. J. Pediat. 56:347-354 (March) 1960 [St. Louis].

Interviews were conducted at the Johns Hopkins Hospital, Baltimore, with 3,361 close relatives of 669 epileptics and with 2,858 close relatives of 470 control patients with epilepsy. A small but significant familial aggregation of idiopathic major epilepsy was demonstrated. This aggregation appeared to vary with the age of the proband at the onset of epilepsy, and was highest when the age of the proband at the 1st epileptic seizure was between birth and 3½ years and between 9½ and 15½ years. No familial aggregation could be demonstrated when the age of the proband at the onset of epilepsy was over 15½ years. No familial aggregation of epilepsy could be demonstrated in any other type of seizure except idiopathic major motor epilepsy. Simple febrile convulsions were not included in this study. Hereditary transmission of epilepsy could not be demonstrated, but it could not be ruled out. Familial aggregation of idiopathic major motor epilepsy may be due to familial perinatal brain injury, to inheritance, or to a combination of these factors. The highest risk of developing epilepsy was found in the close relatives of probands in whom major motor epileptic seizures occurred before the age of 3½ years; in 7.6% of these relatives major motor epileptic seizures may be expected by the age of 19½ years, and in 9.4% by the age of 39½ years. Comparable risks in the relatives of the control patients were 9.4 and 2.3%.

Abdominal Epilepsy. B. N. Sheeby, S. C. Little, and J. J. Stone. J. Pediat. 56:355-363 (March) 1960 [St. Louis].

The authors studied 19 patients with paroxysmal abdominal symptoms. The ages of the patients ranged from 16 months to 35 years; the average age was 11.6 years, and 74% fell between 4 and 13 years. The patients remained under observation for periods ranging from 4 months to 10 years. There was no statistically significant sex predominance. All the patients complained of attacks of paroxysmal abdominal discomfort and/or nausea and vomiting. The symptoms most frequently associated with the pain were postictal somnolence, syncope, or some other disorder of consciousness, such as confusion or lack of awareness of surroundings. Paroxysmal headaches occurred in 26% of the patients. Some type of seizure manifestations was present in 31%. Febrile convulsions occurred in 21%; grand mal seizures, in 16%; and psychomotor attacks, in 16%. Paroxysmal pains in locations other than the head and abdomen were prominent in one patient. The family history showed a rather high incidence of paroxysmal disorders; either migraines or seizures were present in some close relative in 26% of the patients, and peptic ulcer was present in a close relative in 16%. The electroencephalograms were usually abnormal and often showed "14 and 6/sec. dysrhythmia" which is, according to Gibbs, indicative of thalamic and hypothalamic epilepsy.

The duration of the complaints, when the patients were first seen, had varied from 3 weeks to 18 years, with an average of 65 months. The treatment with diphenylhydantoin (Dilantin) sodium has given generally good results. There were sufficient data on 12 patients to estimate the degree of improvement; 5 patients were completely free of attacks, 5 had less frequent attacks, and 2 showed no improvement. Abdominal epilepsy occurs with greater frequency than is generally suspected, and is predominantly a syndrome affecting children. The disorder is generally benign and usually responds well to anticonvulsant medication.

Observations on 500 Cases of Migraine and Allied Vascular Headache. G. Selby and J. W. Lance. J. Neurol. Neurosurg. & Psychiat. 23:23-32 (Feb.) 1960 [London].

The authors report on 300 women and 200 men with extracranial vascular headache, who were seen at the Northcott Neurological Center in Sydney, Australia, in the course of the last 6 years. The ages of the patients at the time of the 1st migraine attack varied between 18 months and 60 years, but 92% of the patients were not older than 40 years when the first attack occurred. A positive family history of migraine-type headaches was obtained in 55% of the patients. Fifteen per cent of the patients gave a family history of epilepsy. An allergic diathesis was found in the family history of 38% of the patients. A personal history of convulsions in childhood, or epilepsy not directly associated with the migraine attack, occurred in 11% of the patients. Thirty-five per cent of the patients gave a history of allergic disorders. There was no significant difference in the associated clinical phenomena, whether the headache was hemicranial or of generalized distribution. Impairment of consciousness was more common in patients in whom attacks were accompanied by other symptoms of cerebral dysfunction. Electroencephalographic recordings were obtained from 459 patients, and about 30% of these patients had abnormal records, irrespective of the association of focal cerebral disturbances with the headache. If only patients, aged

13 years and over, were considered, 26% were observed to have abnormal records, the percentage being higher for female than for male patients. Roentgenograms of the skull were taken from 453 patients, and carotid angiography was performed on 17 in whom there was clinical suspicion of focal intracranial disease; all the angiograms were normal.

The results of these examinations and the history of the patients reaffirm the generally held opinion that there is no single cause for vascular headache. Heredity and personality structure, however, provide the common background, with an allergic diathesis contributing in about 33% of the cases. The association with epilepsy and abnormal electroencephalographic tracings indicates that cerebral dysrhythmia must be considered as one causative mechanism. General instability of the autonomic nervous system manifests itself from infancy in attacks of cyclic vomiting, proneness to travel sickness, and fainting, and participates extensively in the actual migraine attack. The constriction of intracranial vessels and the dilatation of extracranial vessels may be only facets of the basically disturbed vasomotor control, but the authors feel that this disturbance extends beyond the cranial circulation and involves the peripheral vessels. The effect of psychological factors in triggering attacks is not surprising in view of the importance of the autonomic nervous system as the somatic mediator of the emotional state. It has remained unexplained why single intracranial vessels should be selectively involved, producing a recurrent pattern of cerebral disturbances which may be constant for a particular patient.

Epilepsy, Light-Sensitivity and Left-Handedness in a Family with Monozygotic Triplets. K. M. Herrlin. Pediatrics 25:385-399 (March) 1960 [Springfield, Ill.].

A family, consisting of monozygotic 14-year-old male triplets, their older brother, and their parents, was examined at the neurological clinic, Serafimerlazarettet, in Stockholm. One triplet is right-handed, and the other 2 are left-handed, as are several relatives on the father's side. After an analysis of the probable course in cleavage of the embryos, the hypothesis is advanced that the different handedness is probably due to a mirror-image mechanism in cleavage of one or possibly of both embryos. It is suggested that such a mechanism can also explain the reversed asymmetry in the papillary pattern of the triplets' hand prints in the hypothenar region. In the mother, myoclonic jerks are elicited by intermittent sunlight; during photic stimulation with the stroboscope, they are synchronous with the light flashes. The older son has photogenic epilepsy; in him, as in the triplets, intermittent light flashes from the stroboscope elicit a clinical seizure. It is postulated that the sensitivity to light in this family is due to a probably dominant, genetically determined cerebral dysfunction, which can be manifested clinically in different ways.

Studies on Locomotor Syndromes of Possible Psychogenic Origin: II. The So-called Barré-Lieou Syndrome. J. Rotés-Querol, P. B. Crespi, and A. C. Puiggrós. Med. clín. 33:235-242 (Oct.) 1959 (In Spanish) [Barcelona, Spain].

Sixty-four patients among 3,307 observed in the department of rheumatology, Faculty of Medicine. in Barcelona, presented symptoms characteristic of the syndrome described by Barré in 1926 and by his disciple, Lieou, in 1928. There were 49 female and 15 male patients in this series, with ages ranging from 16 to 66 years and a peak incidence in the 36-to-45-year age bracket. The most frequent complaints were headache, vertigo and nausea, tinnitus, sensation of heaviness or pain around the eyes, paresthesia, and muscular weakness. In most patients these symptoms disappeared at night, during their sleep, to reappear the following morning. The interval between the onset of symptoms and the examination at the rheumatologic clinic varied between 1 and 20 years.

Physical examination revealed only slight alterations in the spine of 38 patients. Cervical arthrosis was found by roentgenographic study in only 18 patients. Laboratory tests gave normal results in almost all the patients. The contrast between the number of complaints and the absence of findings by physical, laboratory, and roentgenologic examinations, together with the presence of personality and emotional disorders in a number of patients, led the authors to the conclusion that there is a certain relationship between this type of neurosis and the clinical syndrome. The treatment given the 64 patients studied consisted mainly of psychotherapy, to which the administration of sedatives was added. The authors believe that the good results obtained in a large number of patients confirm their notion that the psychic element is fundamental in the etiology of the so-called Barré-Lieou syndrome.

Pyruvate Metabolism in Diabetic Neuropathy. R. H. S. Thompson, W. J. H. Butterfield, and I. K. Fry. Proc. Roy. Soc. Med. 53:143-146 (Feb.) 1960 [London].

There is no clear evidence to support the suggestion that diabetic neuropathy is mainly due to an accompanying thiamine deficiency. It is, however, now known that the underlying biochemical lesion in thiamine deficiency, namely, a block in the normal oxidative pathway of pyruvate metabolism inside the cells, can be produced by a variety of causes other than thiamine deficiency, and that certain of these other causes can also manifest the block in pyruvate metabolism by bringing about the development of a peripheral neuritis closely resembling that due to a thiamine deficiency. For example, arsenical polyneuritis is now known to be associated with an inactivation of certain of the enzyme-coenzyme systems concerned in the oxidation of pyruvate, this inactivation resulting from a chemical interaction between the arsenical compounds and certain essential sulfhydryl (SH) groups in the enzyme system.

Studies were made also on the blood pyruvate levels in patients with diabetic neuropathy. High pyruvate blood levels were found no more frequently in diabetics with neuropathy than in those without it. So that, just as there is little evidence of any association with thiamine deficiency, there is as yet no clear evidence that diabetic neuropathy is due to any other type of impairment of pyruvate metabolism. At the same time, it is now known that many diabetics have a demonstrable abnormality of pyruvate metabolism, and that the methods of analysis of venous blood from the forearm are relatively crude for the investigation of chronic, and perhaps only slight, biochemical changes in nerve cells, and they may have to be refined still more before one can exclude a defect in oxidative metabolism in nerve cells in diabetic neuropathy.

At present one can only theorize as to why peripheral neuropathy should develop in some patients and not in others. Abnormalities in the lipid metabolism in diabetes may play a part, and the raised blood sugar level may affect nervous excitability. Finally, there may circulate in certain types of diabetes an alloxan-like substance, possibly derived from a derangement of purine metabolism. Since alloxan is a powerful SH inhibitor, and since it is known that SH inhibitors can produce neuropathies, the presence of an alloxan-like substance not only might account for beta-cell damage, but also might explain why in some patients neuritic symptoms develop so early in the disease.

GYNECOLOGY & OBSTETRICS

Sarcoidosis of the Uterus. A. B. Taylor. J. Obst. & Gynaec. Brit. Emp. 67:32-35 (Feb.) 1960 [London].

Two cases of sarcoidosis of the uterus are reported, in which the diagnosis, from uterine curettings, was mistaken at first for tuberculosis. Only 8 other cases have been found reported in the literature, but the disease may not be as rare as it seems. The differentiation of the 2 diseases may be difficult, and tuberculosis is only certain with bacteriological proof. The concomitant lesions of sarcoidosis—uveoparotitis, lung infiltration, enlarged mediastinal and other nodes, a negative tuberculin reaction, reversed blood albumin-globulin ratio, and a positive Kveim test—may help in making the diagnosis. The correct diagnosis is important, as antituberculous chemotherapy is not needed, and the prospect for further pregnancy is not excluded. Cortisone treatment for uterine sarcoidosis has not been reported before, but it should be employed, as in lesions elsewhere, if there are symptoms or if damage from resultant fibrosis is expected.

The Value of Colposcopy in the Detection of Preclinical Carcinoma of the Cervix: Three Years' Experience at King George V Memorial Hospital, Sydney. M. Coppleson. J. Obst. & Gynaec. Brit. Emp. 67:11-23 (Feb.) 1960 [London].

The first 3 years' experience with colposcopy at the King George V Memorial Hospital, Royal Prince Alfred Hospital, of Sydney, Australia, where 1,000 colposcopic examinations have been carried out to date, is discussed. Cytology and colposcopy made possible the discovery of 11 totally unsuspected carcinomas of the cervix, which would have otherwise been missed. There have been some other cases. Colposcopy either has been directly responsible or has played an important part in the detection of 7 of these cases. These include 1 preinvasive cancer (stage 0), 1 cancer with questionable invasion, and 5 cancers with early invasion. Such cases have been termed "preclinical carcinoma," as they would not have been detected by traditional methods of examination. The 11 cases constituted 4.5% of the 242 carcinomas of the cervix treated at this institution during the same period.

None of the patients in this series had any clinical signs suggestive of carcinoma of the cervix, and many of them had been examined in the preoperative clinic by a panel of 3 gynecologists. Cytology and colposcopy were performed after a provisional benign diagnosis, such as fibroids, uterine prolapse, functional uterine hemorrhage, or cervical erosion, had been made in all the cases. In no case was cervical biopsy originally recommended. Two patients had suspicious colposcopic findings, but, in view of a negative Papanicolaou smear and the benign appearance of the cervix to the naked eye, the originally recommended operation was performed without delay. The diagnosis was made later on examination of the surgical specimens. In 3 cases both methods suggested the presence of cervical carcinoma. Cytology was positive, and the colposcopic examination, performed in ignorance of the result of the smear, showed suspicious areas necessitating biopsy. These cases underlined another important function of the colposcope, that of selecting the optimal site for biopsy. All these carcinomas were small and corresponded to the only suspicious colposcopic areas on the cervix. In 2 patients the carcinoma was no more than 1 cm. in diameter and could have easily been missed by biopsy. On 4 occasions the colposcopic findings were highly suggestive of carcinoma, but the initial cytology was negative. In one of these cases a recheck of the smear showed carcinoma cells. In the other 3 cases positive cytology suggested the presence of carcinoma. In only one of this group was a colposcopic examination carried out, but no suspicious changes had been detected in the cervix. The author points out the value of the complementary use of colposcopy and cytology in the early detection of carcinoma of the cervix.

Aortic Hypoplasia and Its Significance in the Etiology of Pre-Eclamptic Toxaemia. C. A. B. Clemetson. J. Obst. & Gynaec. Brit. Emp. 67:90-101 (Feb.) 1960 [London].

Investigation of women after severe early or recurrent preeclampsia by aortography, with use of Seldinger's percutaneous femoral catheter technique, has revealed that 5 out of 8 of these women had aortic hypoplasia; the other 3 were found to have excessive responses to the cold pressor test. These findings are taken as evidence in favor of the placental ischemia theory of the etiology of preeclampsia. Presacral neurectomy has been used in an attempt to improve the uterine blood supply in women with arterial hypoplasia. The results obtained in 3 women, who have since become pregnant, are encouraging. Oral medication with a combination of hydralozine (Apresoline) and reserpine (Serpasil) has been used for women with labile hypertension who have had unsuccessful pregnancies, and it is recommended that this treatment should be started in anticipation of a future pregnancy.

Carcinoma of the Breast Associated with Pregnancy or Lactation. R. C. Austin Jr. Obst. & Gynec. 15:287-291 (March) 1960 [New York].

This is a review of the world literature and of the observations made on 9 patients with carcinoma of the breast, associated with pregnancy or lactation, who were treated at the Medical Center of the University of Colorado during the past 10 years. It shows that the over-all prognosis in such patients is poor. In 8 of the 9 patients reported, the disease had spread to the axillary nodes when treatment was started; none of these patients survived 5 years. The remaining patient had a lesion localized in the breast and is living, without evidence of disease, 8½ years after therapy. Most of these patients had been referred to the center either after long patient-and-physician delay or after primary treatment elsewhere.

The data suggest that a 5-year survival rate may be expected in 60 to 70% of those patients in whom the disease is localized, while such survival is expected in 6% of the patients in whom spread to the axilla has occurred. There is evidence that carcinoma of the breast metastasizes much more rapidly in the course of pregnancy or lactation. Thus, it is essential to diagnose carcinoma of the breast in pregnant patients before it has spread. Radical mastectomy is the procedure of choice if the lesion is operable, and should not be delayed because of pregnancy. Biopsy should be immediately performed on any lump or suspicious area which persists despite treatment. Subsequent pregnancies should be advised against for at least 3 years, if the disease is localized in the breast, and for 5 years, if there is spread to the axillary nodes. Immediate termination of pregnancy in the presence of carcinoma of the breast would increase the 5-year survival rate. Oophorectomy should be performed only as a therapeutic measure; if there is evidence of spread, it may be performed at the time of primary treatment.

Placenta Previa Accreta. G. S. Foster. Obst. & Gynec. 15:322-328 (March) 1960 [New York].

Placenta previa accreta is an uncommon condition which accounts for 18% of all the cases of placenta accreta. The author reviews 44 cases of placenta previa accreta described in the literature and also describes in detail 2 cases which occurred among 19,500 deliveries at hospitals in Cardiff, Wales. Several etiological factors have been incriminated, including previous endometrial injury, such as cesarean section, curettage, and manual removal of the placenta, as well as implantation in areas of endometrial deficiency, such as the lower segment and the cornu. From this study it appears that (1) the mortality among those patients undergoing vaginal delivery was greater than among those undergoing abdominal cesarean section, and (2) the mortality increased when hysterectomy was not performed. Abdominal hysterectomy should be performed on patients in whom placenta previa accreta is encountered during the 3rd stage after vaginal delivery; conservation of the uterus is dangerous under these circumstances.

PEDIATRICS

Study of 104 Exsanguination Transfusions on Newborn Infants with Fresh Heparinized Blood. M. P. Leroux, J. Guimbretière, and H. Harousseau. Presse méd. 68:435-437 (March 5) 1960 (In French) [Paris].

A new technique of exsanguination transfusion has been developed by the authors, heparin (Liquaemin) sodium being used as the only anticoagulant. The contents of a 25-mg. ampul of heparin are diluted in 24 cc. of isotonic sodium chloride solution, which gives a precise titer of 1 mg. of heparin per 1 cc. of the mixture. Amounts of 300, 350, or 400 cc. of fresh blood require, respectively, 8, 9, or 10 cc. of the heparin solution to prevent coagulation. As the blood is withdrawn from the donor, the container is shaken to make the mixture with the heparin solution homogeneous. A catheter is placed in the umbilical vein of the patient, and 1.5 mg. of heparin (1.5 cc. of the solution) is injected. The exsanguination is then carried out in the usual manner, with a 3-way fawcet syringe, and a transfusion tube with filter placed between the blood container and the syringe fawcet. At the end of the operation the circulating heparin is neutralized with protamine sulfate.

One hundred four newborn infants with erythroblastosis due to fetus-mother blood incompatibility were treated by the new technique. The average duration of the procedure was one hour, and in 103 patients the transfusion developed without any difficulty imputable to the method. On the average, the amount of blood transfused was 750 cc.; the circulating heparin, 15 to 20 mg.; and the quantity of protamine sulfate solution used, 1.5 to 2 cc. The new method prevents the toxic accidents caused by citrated blood, by hypocalcemia, and by embolism due either to the formation of clots or to the successive disobstructions which are necessary when disodic citrated blood is used. The repetition of the transfusion, if needed, is made easier by this technique.

Observations on 100 Cases of Leukemia in Childhood. R. Lightwood, H. Barrie, and N. Butler. Brit. M. J. 1:747-752 (March 12) 1960 [London].

The authors report on the treatment of 100 children with leukemia at the Hospital for Sick Children in London. The types of the disease were acute undifferentiated-cell leukemia in 92 patients, acute monoblastic in 5, chronic myeloid in 2, and plasma-cell in 1. The commonest symptoms at the time of admission to the hospital were pallor, limb pain, and bruising; the most frequent signs were fever, lymphadenopathy, and hepatosplenomegaly. The total white blood cell count was normal in nearly one-half of the patients, while leukopenia was present in 25%, and leukocytosis in 30%. Abnormal white blood cells were found in the initial peripheral blood count in 58%; radiologic bone changes occurred in two-thirds of those who were x-rayed, the tibia and the femur being the most frequently involved bones.

Sixty-three patients were treated with one or more courses of steroids, aminopterin, or mercaptopurine. The average survival time increased progressively from 5.5 months, when steroids only were given, to 13.3 months when all 3 antileukemic agents were used. All the untreated children died within one year, at which time nearly one-fourth of the treated group was still alive. The longest survival was 30 months, observed in a 5-year-old boy with acute undifferentiated leukemia, who had 5 remissions, the highest number obtained in this series. Thirty-four patients (54% of the treated group) had at least one complete remission, and 14 (22%) obtained partial remissions.

Steroids were found to be the most effective and rapidly acting drugs, especially in acute stages with thrombocytopenia and anemia. For rapid action, steroids were given intravenously in the form of hydrocortisone or corticotropin. After a patient had become apparently resistant to cortisone, a further remission was sometimes obtained by an increase in dosage to 300 or 400 mg. daily, or by a change to one of the newer derivatives of corticotropin. A dose of cortisone, smaller than 200 mg. daily, failed to obtain a satisfactory remission rate. The results observed in this study suggest that it is reasonable to combine an antimetabolite with cortisone in certain cases of acute leukemia, when there is leukocytosis, polymorphonuclear predominance in the peripheral count, or a very short clinical history. It is also suggested that the administration of antimetabolites should be started in patients being treated with steroids when the initial fever fails to subside within 3 days of the beginning of the therapy.

The authors believe that the remission therapy described lengthens the patients' life and changes the clinical course of the disease. It may also affect the pathology, since with increased survival of patients with acute leukemia symptoms of meningeal syndrome and of kidney enlargement have become more frequent. In this series there was one patient with symptoms and signs of meningeal involvement, and several patients manifested neurological signs. Kidney enlargement was observed at autopsy in 18 out of 24 treated patients, as compared with 5 out of 19 untreated patients.

Action of Vitamin D: Clinical Use. V. G. Fanconi. Helvet. paediat. acta 14:462-471 (Dec.) 1959 (In German) [Basel, Switzerland].

Certain effects of vitamin D are dependent on the original condition of the organism. The mineral transfer between bone and serum always takes place in both directions at once, and the direction in which the action of vitamin D predominates is determined by the quantity of calcium that can be absorbed from the intestine. The modification of the renal excretion of phosphates by vitamin D is likewise dependent on the existing condition. If the clearance of phosphate is increased, as in the presence of rickets, vitamin D will improve the tubular reabsorption; if, however, there is a stasis of phosphate, as in rachitogenic tetany or in hypoparathyroidism, vitamin D will increase the excretion of phosphate. The effect of vitamin D may also depend on the dose. In the vitamin D deficiency of rickets, small doses may favor bone mineralization, but the calcium and phosphorus content in the serum may be changed in such a way that tetany develops. However, massive doses of vitamin D improve the calcium resorption from the intestine to such an extent that it is adequate for the needs of the bones as well as for the maintenance of the calcium level of the serum.

Case histories are presented to show that vitamin D deficiency may cause secondary hyperparathyroidism and tubular disturbances. Most cases of renal rickets and of hypoparathyroidism show a good response to vitamin D in high doses. Furthermore, a case of severe rickets associated with a benign tumor of a rib is mentioned. After removal of the giant-cell granuloma from the rib, rickets healed without the administration of vitamin D.

In commenting on excessive dosage and on hypersensitivity to vitamin D, the author shows that for the practitioner it is of vital importance to know whether a child will need or tolerate high doses of vitamin D or whether it is hypersensitive to the vitamin. Reduced sensitivity exists, and, therefore, high doses are required in children with familial rickets, with aminoaciduria, and during periods of accelerated growth. Increased sensitivity exists in children with retarded growth, particularly when endocrine disturbances exist. Vitamin D should not be given to children in whom the metaphysial plates are of greater than normal density. Children with premature closure of the fontanels or of the cranial sutures are hypersensitive to vitamin D. In children without endocrine deficiencies, immobilization may lead to hypersensitivity to vitamin D and to D hypervitaminosis; the author observed this in a boy who had osteochondrosis of the femoral capitular epiphysis (Perthes' disease).

Phosphate Metabolism in Rickets and Tetany. J. H. P. Jonxis. Helvet. paediat. acta 14:491-496 (Dec.) 1959 (In English) [Basel, Switzerland].

Rickets or tetany develops in a child who does not obtain, or cannot produce, an adequate amount of vitamin D. The parathyroid glands may play a part in the disturbances of the calcium and phosphate metabolisms in children with vitamin D deficiency, since these glands are often in a state of hyperactivity in rachitic children. This has led to the assumption that the biochemical disturbances in the rachitic child are partly due to hyperparathyroidism. However, it is not known whether the amount of the hormone that is released by the hyperactive gland is really increased. There is a possibility that the hormone cannot display its normal action because of lack of vitamin D, which vitamin might be necessary for the normal action of the hormone. This latter supposition is suggested by the decreased reaction of vitamin-D-deficient children to parathormone administration.

The author administered phosphate by mouth to rachitic children before and after treatment with vitamin D. The results of studies in these children support the theory that vitamin D is necessary for the normal action of parathormone. As a result of diminished response of the bone cells and of the tubular cells of the kidney to parathormone, the parathyroids will get into a state of hyperactivity without being able to compensate the metabolic defects caused by the lack of vitamin D in rachitic children.

Idiopathic Hypercalcemia of Infancy and Vitamin D Metabolism. F. X. Fellers, Helvet. paediat. acta 14:483-490 (Dec.) 1959 (In English) [Basel, Switzerland].

Fellers is concerned with a severe form of infantile hypercalcemia, which he observed in 3 infants. The following findings in these infants can be attributed to excessive effects of vitamin D: hypercalcemia, increased calcium absorption from the intestine, renal damage, elevation of serum citrate, retardation of growth, increased renal phosphate reabsorption, and increased serum vitamin-D-like activity, as measured by the standard rachitic rat bioassay procedure. The natural course of the disease would seem to depend on the degree of damage suffered as a result of the persistent hypercalcemia. Survival of children with the severe form of hypercalcemia has been reported, with reversal of the bone changes and return to normal serum calcium levels. The kidney damage and the growth and mental retardation have persisted. In the more benign form the management with low-calcium and low-vitamin-D intake, with adjunctive steroid therapy and calcium binding chemicals, has resulted in recovery without evidence of permanent renal or growth impairment. Removal of dietary vitamin D does not suffice as the only measure.

In the 3 infants the author observed, there was no significant change in the elevated serum vitamin-D-like activity up to 12 months after removal of exogenous vitamin D. Then a low calcium intake was instituted. A protein hydrolysate, with added corn oil, dextrose, starch, and inorganic salts, was given as the principal food, in place of milk, to 2 infants, while the 3rd child received a special low-calcium milk. Clinical improvement occurred within weeks with return of the serum calcium to normal values. During 2 years on this low-calcium intake there was gradual improvement in the radiologic studies of the bones with return to a normal appearance. In the 1st infant, who had been on the low-calcium intake the longest, estimation of the serum vitamin-D-like activity was found to be in the normal range after 26 months of minimal exogenous vitamin D and 19 months of low-dietary calcium. Later, because the development of the late decrease in serum vitamin-D-like activity in the 1st infant suggested a decreased deactivation of vitamin D substances as a possible factor, the fate of intravenously administered vitamin D_3 was studied. Some preliminary data obtained from the use of a radio carbon labeled vitamin D_3 in growing rats are presented. It is deduced that, in some infants with idiopathic hypercalcemia, the defect may be a decreased rate of inactivation of vitamin D substances in the body. The data obtained in rats would suggest that the liver would be the source of this process and presumably through some enzyme system.

Ascending Thrombosis Involving Inferior Vena Cava and Renal Veins. W. T. Bruns. A. M. A. J. Dis. Child. 99:276-281 (March) 1960 [Chicago].

A case of an ascending venous thrombosis in a 12-month-old boy is presented, with a thrombus extending from the great saphenous vein to the proximal end of the infrahepatic portion of the inferior vena cava. Bilateral renal vein thrombosis with hemorrhagic infarction of the kidneys was part of this extensive involvement. The boy, who had fallen headfirst from a height of 3½ to 4 ft., striking the left frontoparietal area of his head on a cement floor, was admitted to the Salt Lake County General Hospital, in Salt Lake City, by reason of sudden onset of left-sided seizures, which developed into complete paralysis of the entire left side of the body. The patient became more alert on the 2nd hospital day, and the paralysis changed into a hemiparesis which improved further over the next days without disappearing completely. Laboratory findings were normal. Phenobarbital was the only medication given. On the 3rd hospital day a moderate nuchal rigidity appeared. A repeated lumbar puncture was again within normal range and showed no bacterial growth. An electroencephalogram obtained on the 5th hospital day was "grossly abnormal," and the white blood cell count increased. The left leg showed some spasticity. A lumbar puncture obtained on the 6th day revealed manometric readings of 360 mm. water without other signs of increased pressure, and bilateral frontal trephination was performed to rule out the possibility of a subdural or extradural hemorrhage. The dura and cortex were found to be macroscopically normal. Prior to this procedure, a venesection on the left lower leg, with insertion of a polyethylene tubing into the greater saphenous vein, had been performed, and the patient, whose hemoglobin value had been 9 Gm. per 100 cc., received 150 cc. of Rh-negative citrated blood. On the 8th hospital day the polyethylene tubing of the venesection had to be removed (52 hours after its application), because the leg appeared red and swollen. Distended lateral, and subsequently midanterior, abdominal veins were noticed, which increased gradually in size. Edema of both lower extremities accompanied this rapidly developing finding. Three days later signs and symptoms of renal vein thrombosis were noticed, with hematuria, albuminuria, oliguria, and a palpable abdominal mass, which, in turn, were followed by an intra-abdominal tumor on the opposite side and anuria of 10 days' duration. The diagnosis of an inferior vena cava thrombosis was supported by a venogram with injection into the greater saphenous vein of the right leg. The patient's condition grew worse. Terminal bronchopneumonia developed, and the patient died 41 days after his admission.

Autopsy revealed an obstruction of the entire vena cava. The thrombus extended into the left renal vein. The right renal vein contained fresh red thrombus. The infrahepatic portion of the inferior vena cava was filled with fresh pale thrombus. The right kidney was larger and completely infarcted while the left kidney which was smaller showed a less complete and older infarction. Extensive thrombosis of cortical veins over the entire cerebrum bilaterally was found, which is difficult to explain. It is suggested that the cerebral vein thrombosis may have developed shortly after, or simultaneously with, the phlebothrombosis in the left leg.

Needle Biopsy of the Liver in Infancy and Early Childhood. D. Stowens. Am. J. Gastroenterol. 33: 294-304 (March) 1960 [New York].

The author reports on 1,000 infants and children with various diseases, on whom needle biopsies of the liver were performed after admission to the Childrens Hospital of Los Angeles. Nine hundred forty-seven patients were between the ages of 1 week and 6 years, and 53 were over 6 years of age. Seven hundred thirty-two patients had jaundice, and 521 of these also had an increased size of the liver; 75 patients had isolated hepatomegaly, and 71 had an increased size of the liver with associated generalized disease. The remaining 122 patients had other complaints, among which were fever of unknown origin and a localized hepatic mass. In 31 of these 122 patients the needle biopsy was performed for research purposes, and in an additional 13 in a "last ditch" effort to arrive at a diagnosis. In almost all the patients a standard series of liver tests were performed. It was found impossible to correlate the results of these tests with the clinical manifestations of the disease. In sharp contrast to the results obtained by laboratory and clinical studies, by the means of which many diseases of the liver in childhood are indistinguishable, needle biopsy of the liver, when employed as a diagnostic technique, proved to be effective in establishing a diagnosis. It is safe and inexpensive. Needle biopsy of the liver proved especially valuable in the diagnosis of congenital malformations of the biliary system in early infancy, and proved a reliable guide in the differentiation of the operable from the inoperable varieties of these malformations. Of the 278 patients with congenital biliary atresia, this diagnosis, made by biopsy, was later confirmed at either autopsy or surgery in 277.

In one-third of all the patients with signs and symptoms of liver disease in infancy or early childhood, current knowledge and techniques are inadequate to determine the nature of the illness. Needle biopsy cannot be expected to be a source of additional information in all of these, for in about half there are no anatomic counterparts to the physiological disease. The feasibility of needle biopsy of the liver as a research tool and as a means of studying diseases of children other than those of the liver is suggested.

DERMATOLOGY

A New Form of Scalp Ringworm in Western New York. J. T. Crissey and R. Martin. New York J. Med. 60:679-682 (March 1) 1960 [New York].

The authors report on 26 patients, between the ages of 2 and 25 years, with tinea capitis caused by Trichophyton tonsurans, who have been seen in the Buffalo area of western New York and in a nearby section of the Ontario peninsula since 1957. This cause of ringworm to the scalp is new to this area. The signs of tinea capitis caused by T. tonsurans are not so easily recognized as those of tinea capitis caused by Microsporum audouini and M. canis. The disease may resemble the Microsporum form or may mimic other diseases of the scalp; infected hairs do not fluoresce under Wood's light, making its detection in schools a serious problem. T. tonsurans produces an endothrix infection in the hair, which is to say that the spores are produced within the substance of the hair cylinder and not outside, as is the case with ordinary Microsporum ringworm. Culture on Sabouraud's medium is necessary for exact identification. Colonies are white to yellow, powdery, and convoluted. This contagious disease, which may occur in children and adults and does not disappear at puberty, is transmitted from person to person directly or through the medium of theater seats, headgear, beauty parlors, and barber shops. Animal vectors play no significant role.

In those few patients who show a marked inflammatory response, such as kerion, conservative management may suffice, since such inflammation indicates a basic change in the host-parasite relationship which will result in a spontaneous cure. In the ordinary noninflammatory case, however, a spontaneous cure is not to be expected. Epilation of the scalp by roentgen rays, with careful manual epilation of the hairs remaining in the follicles, was until recently the preferred treatment for the noninflammatory type of tinea capitis caused by T. tonsurans. The excellent results obtained with the new antibiotic, griseofulvin, would seem to indicate that this drug will replace roentgen-ray epilation as the preferred treatment for all forms of scalp ringworm. Alertness on the part of the physician, particularly if he deals with children, will be necessary to check its spread.

Photographic Evidence of the Spontaneous Involution and Disappearance of Pigmented Nevi: Case Report. W. B. Shelley. A. M. A. Arch. Dermat. 81:208-209 (Feb.) 1960 [Chicago].

Patients sometimes assert that moles have faded away, and recent studies have indicated that older patients have fewer nevi than younger persons do. Nevertheless, specific data on specific lesions are scarce. The author presents the case of a youth in whom he obtained photographic evidence of the spontaneous disappearance of one nevus and the involution of others on the face. At the age of 13 years, this youth was seen by the author for evaluation and treatment of multiple pigmented lesions of his face and neck. According to the history, these had been present since birth. Some were showing growth activity coincident with puberal changes. A photograph taken at the 1st visit showed about 30 lesions, which could be identified clinically as pigmented nevi, and removal of the uppermost lesion on the left cheek permitted histological confirmation. Nests and strands of melanocytic nevus cells were found in both the epidermis and the corium. After an interval of 4 years, the patient was seen again, and the old photographic records were secured for study. It became apparent at once that the large dark nevus on the anterior lower right cheek had completely involuted. Furthermore, it could be seen that all the nevi were spontaneously disappearing. Each was appreciably smaller and less pigmented, although the patient had received no treatment, nor had any leukodermatous changes been observed.

The Private Dermatologist and Skin Cancer: A Clinical Study of 276 Epitheliomas Derived from Five Dermatologic Practices. R. J. Ferrara. A. M. A. Arch. Dermat. 81:225-234 (Feb.) 1960 [Chicago].

The cases with which this report is concerned were drawn from the private practices of 5 Detroit dermatologists. The cases represent patients from the average practice of dermatology, not selected groups from large dermatological centers. The cases were taken in sequential order from pathology files, and in each case the diagnosis was proved by microscopic examination. All the patients were treated prior to July, 1950. A total of 226 epitheliomas occurring in 186 patients were analyzed, and the clinical aspects, treatment, and results of 5 or more years' follow-up were correlated.

There is no optimal therapeutic method for all skin cancers. Fortunately, since the vast majority of skin cancers are superficial, they can be eradicated in a number of ways, including scalpel surgery, electrosurgery, chemosurgery, and irradiation therapy. Certain cases, however, may warrant the use of one particular type of therapy. For example, an infiltrating epithelioma having pseudopods may be in continuity with mucous membranes of the mouth, nose, ears, eyelids, or anogenital area. Such lesions may be mishandled with superficial roentgen-ray therapy or with scalpel surgery, and a destructive form of therapy may be necessary to give the patient the best chance of survival, irrespective of the cosmetic result. Plastic repair can be used later, if necessary, to produce a satisfactory cosmetic result. Lesions over cartilage, bone, and tendon, generally speaking, should best be treated by wide scalpel surgery or electrosurgery. Because of the poor blood supply in these areas, a cancerocidal dose of radiation may lead to necrosis and ulceration, with failure to heal for many months. To manage all types of cutaneous cancers, one must have a thorough knowledge of skin cancer and the various methods of treatment that are available.

After 5 years 206 (94.5%) of all the epitheliomas were clinically cured. The percentages of cures were 95.5% with scalpel surgery, 94.9% with electrocoagulation and curettage, and 93.9% with x-ray therapy. The 5-year cures were 100% in 19 patients treated with electrocoagulation and curettage plus x-ray therapy. In general, it is not so much the particular method of treatment which is of greatest importance, but the training, experience, and ability of the physician applying the method. The author feels that the special knowledge and skill possessed by trained dermatologists in the diagnosis and management of skin cancer merit more recognition.

OPHTHALMOLOGY

The Probable Role of Benign Histoplasmosis in the Etiology of Granulomatous Uveitis. A. C. Woods and H. E. Wahlen. Am. J. Ophth. 49:205-220 (Feb.) 1960 [Chicago].

The concept of histoplasmosis has greatly changed since the introduction in 1941 of histoplasmin as the skin-testing antigen prepared from histoplasma capsulatum. It is now generally accepted that histoplasmosis is rare as a fatal disease in man, but as an unsuspected and asymptomatic infection it is quite commonplace, especially in certain areas.

Histoplasmin tests at the Wilmer Ophthalmological Institute, Johns Hopkins Medical Center, Baltimore, in 1948 had disclosed an unusually high incidence of positive histoplasmin reactions in patients with uveitis. When, in 1951, 2 patients were observed in whom no other cause but histoplasmosis could be incriminated as the cause of uveitis, it was decided to perform intracutaneous tests with histoplasmin in the Wilmer Institute on patients with uveitis, who had pulmonary calcification, and culin negative. In 1953, the uveitis sur- ed, wi plified to include routine histoplasmin tients, regardless of the granulomatous by omatous nature of their uveitis. Except lapses when the supply of histo- hausted, and omissions due to oversight or inability to complete the survey, this ro tine has been consistently followed to date.

This study is based on 186 patients with gran lomatous uveitis and 107 patients with nongra ulomatous uveitis, all of whom have been se since 1951. All have had complete medical surve including histoplasmin tests. In the 186 patier with granulomatous uveitis, there were 62 positi reactors to histoplasmin, and in the 107 patier with nongranulomatous uveitis, there were 16 po tive reactors. This is an incidence, respectively, 33 and 15% in the 2 series. Even after due allo ances were made for the geographic origins of t patients, it was evident that the incidence of po tive reactors in the patients with granulomato uveitis is approximately twice that observed in p tients with nongranulomatous uveitis. Nineteen the 62 patients with granulomatous uveitis show a peculiar and consistent pattern of ocular lesior This pattern consisted of discrete, atrophic, sparse pigmented or unpigmented, peripheral lesions, fc lowed by a later cystic lesion at, or adjacent to, th macula. Approximately one-half of these centr lesions were complicated by a secondary surroun ing hemorrhagic reaction. Nine of these patien showed the trilogy of histoplasmin sensitivity, pu monary calcification, and anergy to tuberculin. I these 9 patients the medical survey had revealed n cause other than histoplasmosis to which the uveit might be attributed. In the other 10 patients th picture was not so clear-cut, but the ocular pictu was characteristic, and the patients undoubted had had a benign systemic histoplasmosis.

While it is, of course, possible that this fund picture may be caused by some other unsuspecte etiological agent, it has thus far been observe only in patients who are hypersensitive to hist plasmin. Based on this evidence, it appears reaso able to assume a cause-and-effect relationship b tween a benign systemic histoplasmosis and thes ocular lesions. There is also some evidence that similar relationship may exist between histoplasm sis and an occasional case of nongranulomato iridocyclitis.

THERAPEUTICS

Vitamin A Deficiency Following Total Gastrectomy J. F. Adams, J. M. Johnstone, and R. D. Hunte Lancet 1:415-417 (Feb. 20) 1960 [London].

The authors report on 4 men, between the age of 42 and 60 years, and a 48-year-old woman, wh had undergone total gastrectomy. This operatio was performed for microscopically confirmed carcinoma in 3 patients, for gastric stenosis due to corrosive gastritis in 1, and for a clinically malignant, but microscopically benign, gastric ulcer in 1. There is good evidence that all these patients had vitamin A deficiency. All had very low serum vitamin A concentrations, and these were raised to normal in the 4 patients who were given vitamin A orally. The defective dark adaptation shown by night blindness in 4 patients was corrected by the oral administration of vitamin A in 3 who were retested. The one patient who had normal dark adaptation had follicular hyperkeratosis, which was cured by the oral administration of vitamin A. None of the night-blind patients were aware of the defect, but this was not unexpected in city dwellers.

The amount of dietary fat absorbed was much impaired in 3 patients, and in the other 2 was just below the usually accepted lower limit of normality. The vitamin A deficiency is of complex origin, and steatorrhea is not the only causal factor. Vitamin A should be administered prophylactically to patients who have undergone gastrectomy. A course of 100,000 I. U. of vitamin A, given daily for 2 weeks every 6 months, seems advisable. On this regimen there is no risk of the toxic effects which might result from large daily doses for long periods.

Artificial Respiration in Severe Renal Failure with Pulmonary Insufficiency. P. Erlanson, R. Lindholm, B. Lindqvist, and A. Swenson. Acta med. scandinav. 166:81-96 (no. 2) 1960 (In English) [Stockholm].

The authors report on the results of artificial respiration administered at the University medical clinic in Lund, Sweden, to patients with renal failure resulting from a serious disease or developing in a postoperative stage. In addition to electrolyte fluid disturbances and uremia, certain complications affect the lung function and cause pulmonary insufficiency, including bronchitis with stagnant secretion, bronchopneumonia, atelectasis, peritonitis, intestinal paralysis, and fluid retention. Sixty-nine patients received artificial respiration at the Lund clinic between 1956 and 1958. Approximately 50% of the patients underwent surgical intervention for different types of disease. The survival rate was 30%, which the authors consider high in comparison with earlier statistics in similar circumstances. Twenty-five cases are analyzed to illustrate the effects of early and late treatment by artificial respiration. Fifteen patients were treated at a relatively early stage of grave pulmonary insufficiency. Eight of them recovered; the remaining 7 patients died of the original disease or of its complications. Ten patients were given artificial respiration at a late stage of grave pulmonary insufficiency. The treatment at this stage prolonged life possibly for a few days but could not prevent a fatal issue.

The diagnosis of pulmonary insufficiency presents some special difficulties, for clinical symptoms may be masked by other signs, such as cyanosis from severe anemia and tachypnea from grave cerebral disorder or muscular fatigue. The indication for artificial respiration must be based primarily on clinical judgment of the extent of pulmonary insufficiency and of its significance in the actual condition of the patient. A pO_2 below 60 mm. Hg in spite of oxygen therapy supports the indication for artificial respiration even if the pCO_2 is not essentially decreased. On the other hand, if there is deterioration of the general condition with increasing symptoms of pulmonary insufficiency, such as tachypnea, tachycardia, shock, and/or coma, artificial respiration is indicated, even if the pO_2 has not decreased below 60 mm. Hg.

A Preliminary Study on the Clinical Use of Choline Salicylate. G. M. Davis, P. T. Moore, J. K. Siemsen, and others. Am. J. M. Sc. 239:273-277 (March) 1960 [Philadelphia].

The authors report preliminary observations on 25 patients with acute rheumatic fever and on 8 with rheumatoid arthritis, who were admitted to the U. S. Naval hospitals in Oakland, Calif., and Great Lakes, Ill.; these patients were given choline salicylate, a new salicylate preparation which is extremely water-soluble in the form of a stable aqueous solution, for periods up to 7 weeks. In the 25 patients with acute rheumatic fever, the daily dose of choline salicylate ranged from 4.8 to 15.75 Gm. Most patients were started on a dose of 10 to 15.75 Gm., which was reduced after 4 to 14 days; the maintenance dose was 11.5 Gm. in 12 patients, 10 Gm. in 7, and 7 Gm. in 6. The drug was given in divided doses every 4 to 6 hours. The clinical and laboratory responses were considered satisfactory in 24 of the 25 patients. Acute polyarthritis was present in 21 patients at the initiation of choline salicylate therapy and subsided completely within 3 to 9 days in 20 patients. Significant elevation of temperature (above 100 F [37.7 C]) was present in 20 patients, and the temperature was restored to normal in 19 patients within 1 to 4 days. The increased erythrocyte sedimentation rate returned to normal within 6 to 34 days. Definite analysis of the response to choline salicylate therapy in the small group of 8 patients with rheumatoid arthritis is impossible, but the responses were altogether comparable to those obtained with equivalent doses of acetylsalicylic acid. Tinnitus and pyrosis were the only side-effects observed. They occurred with daily doses of 7 to 11.5 Gm. of the drug and were mild and readily controlled in 8 of the 25 patients. In 3 additional patients receiving a similar range of doses, these symptoms were severe enough to render reduction of the dosage advisable.

Since critical analysis of the clinical effectiveness of choline salicylate would require more extensive and controlled study on a large group of patients, the impressions based on this preliminary study may be stated as follows. The antipyretic and anti-inflammatory effects of choline salicylate in rheumatic fever appear to be comparable to those of acetylsalicylic acid in corresponding doses, if this series is compared with previous experiences at these hospitals. The anti-inflammatory and analgesic effects of choline salicylate in rheumatoid arthritis appear to be comparable to those of equivalent doses of acetylsalicylic acid. As a rule,

ing blood. Desoxyribonucleic acid-labeling experiments, combined with leukopheresis and other methods of inducing leukopenia and leukocytosis, have shown that granulocytes circulate freely for variable but brief periods, and may be sequestered in various capillary beds for most of their intravascular life. The average time spent in the circulation appears to be between 4 and 8 hours. Once the granulocytes leave the vascular system entirely and migrate into tissue spaces, they do not appear to reenter the circulation in significant numbers.

The marrow granulocyte reserve is the most important factor in the development of an acute leukocytosis as induced by leukopheresis, intravenous bacterial endotoxin, and experimental peritonitis. The adequacy of the marrow granulocyte reserve can usually be assessed by correlation of blood and marrow morphology with the granulocytic response to a purified bacterial lipopolysaccharide, Pyrexal. The response to Pyrexal has been studied in a variety of clinical states, and has been found to be of use in patients with leukopenia associated with Hodgkin's disease or other lymphomas requiring irradiation or other myelotoxic therapy. A normal response is strong evidence for adequate marrow granulocytic reserves. However, the failure to develop a leukocytosis in the normal range must be interpreted in the light of other clinical findings, since it may be due to accelerated removal of cells peripherally, rather than to depletion of the marrow granulocyte reserve.

The physiology of lymphocytes is as yet poorly understood. Present evidence suggests that lymphocytopoiesis may take place in a variety of tissues as well as in lymph nodes, lymph, and blood. It is pointed out that the isotopic data, previously interpreted as showing a long survival time for the mature lymphocyte, may actually reflect the slow turnover by growth of the large mass of lymphocytopoietic tissue.

Persistence of the Left Superior Vena Cava. V. Pecorini, R. J. Macchi, L. D. Suarez, and A. M. Perosio. Prensa méd. argent. 46:2409-2416 (Oct. 2) 1959 (In Spanish) [Buenos Aires].

Two hundred patients with congenital heart disease were observed at the laboratory of hemodynamics of the Instituto de Semiologia, in Buenos Aires, between 1953 and 1958. Heart catheterization showed persistence of the left superior vena cava associated with the basic malformation in 8 patients. This abnormality had not been detected by the physical, radiologic, radioscopic, and electrocardiographic examinations undergone by the 200 patients observed. In 7 patients the left superior vena cava coexisted with the right superior vena cava, and in 1 patient it was the only superior vena cava present.

The authors call attention to the fact that, since the presence of a left superior venan cava raises a technical problem for the use of a lung-heart machine, it is important to detect this anomally before the operation. The ideal methods for diagnosing this malformation are cardiac catheterization and angiocardiography. It is also pointed out that catheterization involves some difficulties, owing to the narrow angle formed by the left subclavian and the abnormal left superior vena cava. Surgical treatment is recommended when there is left-to-right shunt caused by an abnormal pulmonary vein opening into the left superior vena cava, or by the left superior vena cava opening into the left cardiac atrium. There is no need for an operation when the left superior vena cava opens into the right atrium.

Phagocytic Reticuloendothelial Cells in Subacute Bacterial Endocarditis with Negative Cultures. R. W. Hill and E. D. Bayrd. Ann. Int. Med. 52:310-319 (Feb.) 1960 [Lancaster, Pa.].

The authors studied the records of 273 patients with subacute bacterial endocarditis, from whom blood smears were obtained and examined at the Mayo Clinic between 1941 and 1956. The results of blood cultures of 228 of these patients were positive. Of these 228 patients, 176 did not have any reticuloendothelial cells of the phagocytic type in their blood smears. The other 52 patients (23%) did have reticuloendothelial cells in their blood smears, which were actively phagocytic in only 19 patients (8%). This is in contrast to the blood cultures in the remaining 45 patients, which were consistently sterile; blood smears in 15 (one-third of these patients) showed reticuloendothelial cells, with active phagocytosis being noted in 12 (27%). The percentage of reticuloendothelial cells varied greatly from patient to patient and could not be correlated with the amount of phagocytosis. However, reticuloendothelial cells were present in 33% of the patients with sterile blood cultures.

It would appear to be important that one-third of the patients with sterile cultures had these phagocytic reticuloendothelial cells in smears of peripheral blood, and that these cells made up more than 9% of the differential leukocyte count in 9 (60%) of these 15 patients. In contrast, only 2 patients with positive blood cultures had more than 9% reticuloendothelial cells in the differential count. Most diseases with which subacute bacterial endocarditis might be confused are seldom associated with even small numbers of reticuloendothelial cells. Therefore, in considering patients with obscure fever and sterile blood cultures, the authors believe that the finding of this phagocytic type of reticuloendothelial cells in blood smears is most suggestive of subacute bacterial endocarditis. If the number of these cells, whether actually phagocytic or not, exceeds 9% of the differential leukocyte count, it might be best to consider that such patients have subacute bacterial endocarditis, and to treat them accordingly until the diagnosis is proved otherwise.

BOOK REVIEWS

Principles of Public Health Administration. By John J. Hanlon, M.S., M.D., M.P.H., Director of Public Health Services, City of Philadelphia. Third edition. Cloth. $10.50. Pp. 714, with 41 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1960.

It is a significant event when a new edition of this book is printed. The previous two editions have occurred at five-year intervals. New chapters are presently included on, "Social Services and Public Health," "Addictive Diseases," and "The Past As a Prologue." Chapter titles have been changed from "Sociological Aspects of Public Health" to "Behavioral Science and Public Health" and "Cultural Anthropology and Public Health" to "Social Pathology and Public Health." Two chapters, "International Health Programs, Their Growth and Activities" and "The Design of Technical Assistance Programs," have been deleted as such and incorporated into other portions of the book.

The author recognizes that some phases of public health progress are not increasing at their former rate and he states, although not as an explanation of the above, that "most of the health departments' budget is devoted to the salaries of professional workers who serve groups thereof. Nothing is manufactured; practically speaking, the sole product is interpersonal relationships. This being the case, it is only good sense to attempt the delivery of these personal services and interpersonal relationships as close to and as convenient for the consumer as possible." The author also acknowledges other important contributions to public health progress by voluntary organizations, foundations, and, last but not least, the private practitioner of medicine. In speaking of aging and chronic disease he states that the personal approach of the private physician has its limitations and handicaps, not the least of which are the expense and the inadequacy of facilities for early diagnosis and treatment. Inequalities exist in the distribution of members of the healing professions and in such auxiliary aids as hospitals.

In the final chapter, "The Future," the demographic revolution is discussed showing that the lowering of the average age of marriage and parenthood, and the subsequently shorter interval between generations, will result in a larger population for this country, without even a consideration of such factors as increased birth rate and decreased death rate. An interesting new term with future national and international significance is "emporiatrics," the science or the study of the health of the traveler. The word base is emporium (belonging to commerce). It is interesting to consider that whether travel is for pleasure or business it still has economic effects.

One of this author's theses is the justification of public health on the basis of lifesaving, life-prolonging, and resultant economic benefits. In a constructive vein, one does regret that, though the revision includes up-dating such material as grants-in-aid for fiscal year 1959, the Department of Health, Education, and Welfare organization chart dates back to Secretary Oveta Culp Hobby. Since the book is a text on administrative public health, examples of good administration and poor administration are appropriate. We are all in favor of eliminating inefficiency. The author makes a sincere effort to be objective in his evaluation of public health administration and factors relating to it.

Franklin D. Yoder, M.D.

Treatment of Urinary Lithiasis. Compiled and edited by Arthur J. Butt, B.S., M.D., F.A.C.S. Cloth. $21. Pp. 577, with illustrations. Charles C Thomas, Publisher, 3.1-327 E. Lawrence Ave., Springfield, Ill.; Blackell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

This book comprises 30 chapters by individual authors, each of whom has written about one phase of the treatment of urinary calculi. The editor contributed an excellent introductory chapter on the history of the treatment of urinary stones and chapters on the perplexing role of colloid science in their formation and on their quantitative analysis. The history of urinary stones is as old as medicine, and the author has condensed a wealth of material into a fascinating and lucid chapter filled with excellent illustrations. Throughout this volume, the illustrations are of good quality and well reproduced. The medical management of this disease is particularly well presented by several authors, and the chapter by Dr. Snapper is worthy of special commendation.

Although the title implies that treatment is the primary consideration, the text contains much material on etiology and theories of stone formation. Most of the authors concentrated on practical therapeutic aspects but many have also included some statements on history, cause, and pathogenesis. As so often occurs in a volume by many authors, there is much repetition in both the text and the bibliography at the end of each chapter. Since the editor so thoroughly covered the history of each phase of the treatment, he would have been justified in deleting some of this historical material from many of the chapters. Criticism might also be directed towards the comprehensive chapter on preoperative and postoperative care in that it seems too long and all-inclusive for a book such as this. In general, this work brings together in easily readable form all of the phases of its subject in an up-to-date fashion. Much of this material is not currently found in the textbooks of urology, and this volume fills a need by making it readily available under one cover. This book should serve for some time as a standard reference on the subject of calculous disease of the urinary tract, and it deserves a place in the library of anyone treating such patients.

GEORGE J. BULKLEY, M.D.

Your Heart: A Handbook for Laymen. By H. M. Marvin, M.D., Associate Clinical Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut. Cloth. $4.50. Pp. 335, with 1 illustration. Doubleday & Company, Inc., Garden City, N. Y.; 575 Madison Ave., New York 22, 1960.

This is a comprehensive book on the heart from a qualified physician who is a past-president of the American Heart Association. It is a part of the Laymen's Handbook Series developed by the publisher and is an extremely well written book. Indeed, if there could be any adverse criticism it would be that, for the layman, the book is too comprehensive and contains more information than he can digest and much more than he needs. It is definitely a book which can be recommended to intelligent, well-balanced patients who are capable of objective thought. It is not recommended to neurotic or introspective persons or those prone to build up symptom complexes into major disabilities.

W. W. BAUER, M. D.

First Aid: Diagnosis and Management. By Warren H. Cole, Professor and Head of Department of Surgery, University of Illinois College of Medicine, Chicago, and Charles B. Puestow, Clinical Professor of Surgery, University of Illinois College of Medicine. With 16 contributing authors. [Previous title: First Aid, Surgical and Medical.] Fifth edition. Cloth. $6.25. Pp. 420, with 217 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32nd St., New York 1, 1960.

In the opening discussion of precautions and limitations in first-aid work, there is strong emphasis on the inadequacies of lay personnel and the possibility of applying erroneous therapy. It is stated that, nevertheless, complete first-aid therapy is being described for its educational value. This decision might be questioned both on the basis of possible development of frustration in the would-be first-aider and because, with all the details described so explicitly, some first-aiders may forget the initial warnings and attempt to carry out measures that are far beyond their capabilities.

A pertinent example of this borderline area is found in the discussion of tracheostomy, in which the guest writer states that the procedure has occasionally been accomplished by relatively untrained persons using only a pocket knife or razor blade. Further stimulus to impulsive first-aid action is provided by four drawings of the operative steps.

All aspects of first aid are covered in this comprehensive presentation by 16 guest writers and the 2 editors, including care of casualties from missiles, rockets, and nuclear bombs, first aid in industry, and a review of civilian versus military injuries. A high level of reliability is assured, although in certain instances there is some equivocation, as, for example, in the material on possible rabies exposure. Here it is stated that a wound may be swabbed with nitric acid or phenol as soon as possible, but this "is not strongly urged." It is my understanding that this treatment was abandoned long ago. Also, in treatment of boils, local application of sulfathiazole ointment is recommended. This appears contrary to the considered opinion of most therapists. This volume might better be considered a training program or refresher for interested physicians, for which it is eminently appropriate because of its extensiveness and the great detail of treatment that is provided.

WILLIAM W. BOLTON, M.D.

Problems of Etiology and Pathogenesis of Tumors. Academy of Medical Sciences USSR, Institute of Experimental Pathology and Therapy of Cancer. Edited by: Professor N. N. Blokhin. Translated from Russian by U. S. Joint Publications Research Service, Washington, D. C. Symposium on occasion of 70th anniversary of birth and 45th anniversary of scientific, pedagogical, and public activities of Professor A. D. Timofeyevskiy. Paper. Pp. 372, with illustrations. U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Library Russian Scientific Translation Program, Bethesda 14, Md. 1959.

This compilation of the reports presented at the scientific conference of the Institute of Experimental Pathology and Therapy of Cancer of the Academy of Medical Sciences, USSR, in March, 1957, is dedicated in honor of the 70th birthday of Prof. A. D. Timofeyevskiy. It contains the results of the research carried out in the division of the etiology and pathogenesis of tumors, which he directed, and articles written by his former students and colleagues. Timofeyevskiy was particularly interested in the role of viruses in the origin of tumors and used electron microscopy in his studies. These studies revealed the presence of virus-like formations during various stages of cultivation of extracts from human tumors. This volume should be of particular interest to pathologists.

GEORGE HALPERIN, M.D.

Medical Secretary's and Assistant's Handbook. By Besse May Miller. Cloth. $5.75. Pp. 236, with illustrations. Prentice-Hall, Inc., Englewood Cliffs, N. J.; 70 Fifth Ave., New York 11, 1960.

This book is a guide to medical assistants in their role as intermediary between the physician and the patient. The opening chapter defines the intelligent and craftsmanlike profession of the medical secretary. The book examines every phase of her duties, her appearance, deportment, telephone manner, the keeping of medical records, filing systems, and the care of syringes and surgical instruments. Basic advice is given on the medical office itself, such as color schemes, reading material, correct lighting, furnishings for the reception room, and office ho[illegible] There is a résumé explaining how to keep the appointment book, make schedules, establish office routines, take inventories and order supplies, arrange for house visits and hospitalizations, and receive and interview patients.

The book suggests methods for better public relations and offers constructive advice on Blue Cross, Blue Shield, and other forms of medical insurance. The chapter on the doctor and the law contains a digest of medical ethics and tells the secretary what to do with cases that must be reported to the police. The secretarial role is broken down into the various branches of medicine; it covers in turn the general practitioner, the dermatologist, the neurologist, and other specialists. The duties of the secretary are given in each case. A special section deals with the secretary whose employer becomes an author or a lecturer, with practical information on proofreading, copy marking; galley and page proofs, and the scheduling of lecture appointments and traveling arrangements.

The book has a complete index, appendixes of prescriptive abbreviations, definitions of medical terms, and fahrenheit and centigrade comparisons. The many illustrations include sterilization charts, sample forms and records, order and inventory blanks, and even model collection letters. This book covers every aspect of the secretarial role with expert advice and practical suggestions for making the secretary an efficient aide to the doctor.

John H. Talbott, M.D.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P. Sixth edition. Cloth. $8.50. Pp. 751, with 139 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland, 1960.

The scope of this text goes somewhat beyond that of the usual handbook for quick review or reference on medical emergencies. The author includes a good deal of information more often read in the standard textbooks of medicine and surgery. This book, that should be readily available to the practitioner, has the advantage of covering its subject completely.

One feature that is not often found in books on emergency care is advice pertaining to items which concern the patient. For example, under the section on venopuncture the author says, "Don't pinch the skin with the tourniquet. Don't let the antiseptic trickle on the arm—He (the patient) will think that it is blood. Use a sharp needle but don't probe for the vein." These bits of advice make the book a good one for doctors just starting their practice.

Two chapters, Medical Emergencies at Sea and Medical Emergencies in the Air, contain information that should be used more each year as the number of people who handle their own boats and airplanes increases. The author also includes information on situations which often are considered complications of a standard procedure. Many of these complications, such as the needle that breaks off during an intramuscular injection and air embolism from an intravenous infusion, are emergencies.

This book is written primarily for physicians who practice in England. Many British proprietary names not widely used in this country are used throughout the book. The chapter on medicolegal and other nonclinical emergencies does not apply to practice in the United States but does serve to remind the physician that these issues need to be considered.

Theodore Johnson, M.D.

Allergy: What It Is and What to Do About It. By Harry Swartz, M.D., Chief, Allergy Clinic, New York Polyclinic Hospital, New York. [Second edition.] Cloth. $3.95. Pp. 232. Frederick Ungar Publishing Company, 131 E. 23rd St., New York 10, 1960.

This book is addressed, in the words of the introduction, to allergic and possibly allergic persons. The opening chapters are largely historical and include an account of Richet's production of anaphylaxis by nettle poison in dogs. Later chapters classify offending substances as inhalants, ingestants, injectants, infectants, and contactants; describe the common and uncommon manifestations of allergy; and give the theoretical basis for the various methods of treatment now in use. There is an interesting chapter listing some of the many trouble-making materials now used in the home and in industry. The glossary, the weakest part of the book, contains roughly the proportion of obscurities and errors one is accustomed to finding in glossaries. It seems desirable that someone should protest, occasionally, against the prevailing notion among glossary-makers that difficult ideas can be made clear by substituting something vague or inaccurate for the carefully worded definitions that can be found so easily in dictionaries and textbooks. This book lacks illustrations but has a good index.

Frederic T. Jung, M.D.

Diagnosis and Treatment of Diseases of the Trachea and Bronchi. By Herman J. Moersch, M.D., and Howard A. Andersen, M.D. Publication number 389, American Lecture Series, monograph in American Lectures in Chest Diseases. Edited by J. A. Myers, Ph.D., M.D., Professor of Medicine, University of Minnesota, Minneapolis. Cloth. $4.25. Pp. 108, with 35 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

This excellent monograph should be in the library of everyone who treats respiratory diseases. The first chapter, dealing with anatomic aspects, is followed by one on anomalies of the tracheobronchial tree. Various conditions affecting the bronchi, such as acute laryngotracheobronchitis, vascular defects affecting the tracheobronchial tree, and their complications are then examined. Tumors of the trachea, although rare, are also considered. There are chapters on chronic bronchitis, bronchiectasis (which is considered more completely than most of the other subjects), foreign bodies in the tracheobronchial tree, tuberculosis of the tracheobronchial tree, and bronchogenic carcinoma. There are also shorter chapters on alveolar cell tumor of the lung, bronchial adenoma, benign bronchial tumors, broncholithiasis, bronchostenosis, atelectasis, bronchial obstruction by compression, bronchoesophageal and tracheoesophageal fistulas, asthma, syphilis of the tracheobronchial tree, hemoptysis, and trauma. The monograph is written in an easily readable style and can be digested in a short time.

Alton Ochsner, M.D.

Basic Office Dermatology. By Stuart Maddin, M.D., Julius L. Danto, M.D., and William D. Stewart, M.D., F.R.C.P.(C). With forewords by Dr. R. F. Farquharson, M.D., and M. B. Sulzberger, M.D. Cloth. $11.75. Pp. 308, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

At long last something new, interesting, and valuable in the field of dermatology has been printed. The intent of the authors is that the book should be used (1) as a ready reference for the diagnosis and effective treatment of the common dermatoses (the common diseases, listed in section 1, are arranged in clinical groups); (2) to obtain help in unfamiliar cases (by reference to section 3 on regional dermatological diagnosis); and (3) as a guide to the treatment of those patients in whom there is a lack of therapeutic response (section 5).

There is an excellent section on diagnostic procedures and one devoted to multiple organ diseases with cutaneous manifestations, such as lupus erythematosus, sarcoidosis, and porphyria. Dermatological allergy is given its rightful place. The concluding section, "Dermatological Counselling Based on Physiology," includes topics such as scalp and hair, deodorants, antiperspirants, diet, and psychosomatic factors in dermatology.

The selection of paper, binding, and printing are excellent, and the line drawings and photographic illustrations are above the usual quality. There is also a color atlas which leaves one with a feeling that it should have been extended. This book is recommended for the general practitioner who has a limited knowledge of skin diseases, to the young dermatologist who finds his approach confused by the verbiage in the usual manuals and text books on this subject, and to the established specialist because of the succinct style and the illustrations.

Theodore K. Lawless, M.D.

Los Alamos Handbook of Radiation Monitoring. Compiled and edited by Jerome E. Dummer, Jr. LA-1835. Third edition. Paper. 65 cents. Pp. 180, with 39 illustrations. Superintendent of Documents, Govern. Print. Off., 1958.

A primary function of the Los Alamos Scientific Laboratory is the radiation monitoring of the bomb tests. In addition, the Los Alamos staff has the responsibility for monitoring its own work on radiation. Since many persons must participate in the monitoring program, it is necessary to furnish each monitor with a concise compilation of the reference data essential to a good monitoring program. This third edition has been completely rewritten, and hence, brought up to date, by Mr. Jerome E. Dummer Jr., from Los Alamos. The subject matter includes check lists, radio codes, pictures of equipment, and items and policies of protection and monitoring that pertain solely to the Los Alamos situation. The book offers useful methodical hints that would be followed in smaller problems. It also deals with almost every kind of exposure and contamination from radiation and radioactive isotopes. The appendixes and glossary are remarkable for their completeness and accuracy.

There is no bias in this book except that which is stated in the preface. The book was written for Los Alamos monitors. It is well illustrated and well printed but is composed in handbook style and thus is informative only to a person who has had training in radiation monitoring. In the rapidly changing field of radiation protection, this is probably the best concise compilation available. It is a handbook and does not pretend to be anything else.

Marshall Brucer, M.D.

Report on a Visit to the U. S. S. R., Poland and Czechoslovakia to Review Work on Live Poliovirus Vaccine, August-October 1959. By Dorothy M. Horstmann, M.D. From Section of Epidemiology and Preventive Medicine and Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, U. S. A. Paper. Pp. 124, with 33 illustrations. Yale University, Section of Epidemiology and Preventive Medicine, 333 Cedar St., New Haven 11, Conn., 1960.

This booklet reports a visit in 1959 to the U. S. S. R., Poland, and Czechoslovakia. The visit was made under the auspices of WHO in order to evaluate various aspects of the programs of mass vaccination using Sabin's strains of live poliovirus. In the U. S. S. R., about 15,000,000 persons were so vaccinated. All the evidence pointed to the safety of the procedure for the vaccinated persons and the community throughout follow-up periods of six to nine months. A final evaluation of the effectiveness of the oral vaccine could not be made, but the results were regarded as promising. Although no conclusions were drawn from the observation of the programs in Poland and Czechoslovakia, the report stressed the advantage from the standpoint of the epidemiologist of a large controlled population that is used to submitting to orders from government authorities. This booklet must be considered a preliminary report. As such, it should be of interest chiefly to a limited group which would include virologists, epidemiologists, and public health officials. There is no index.

W. G. Brandstadt, M.D.

QUESTIONS AND ANSWERS

COMPLICATED MANIFESTATIONS OF INFECTIOUS MONONUCLEOSIS

To the Editor:—*A 34-year-old woman had infectious mononucleosis with liver involvement. Results of liver function tests, repeated several times, at present are normal except for a serum cholesterol level of 380 mg.%. Roentgenographic studies show that she has a normal gallbladder, upper gastrointestinal tract, and chest. She does have symptoms of biliary dyskinesia, which has been treated with dehydrocholic acid. She has also a hypothyroid status, which has been present for some years, and is treated with administration of 1 Gm. of desiccated thyroid daily. At a time when she should have been well on the road to recovery, she developed a marked anxiety neurosis. There is no apparent reason for the neurosis but her original disease which lasted three months. When answering my questions, assume that she had infectious mononucleosis and no other liver disease: 1. Does a high level of iodine have any known adverse affect on cerebral tissue? 2. To what extent does myxedema or a hypothyroid state affect the brain and contribute to an anxiety condition? 3. To what extent does infectious mononucleosis contribute to this picture? 4. To what extent does an elevated serum cholesterol level contribute to the anxiety? 5. To what extent does an elevated serum bilirubin level (not excessive) contribute to this?*

M.D., New York.

Answer.—In this case it appears not unlikely that some form of hepatitis has been present. In the absence of typical blood findings or a positive heterophil count, it may be difficult to determine whether one is dealing with so-called viral hepatitis or mononucleosis with hepatitis. The clinical picture of the two may be indistinguishable. However, as requested, it will be assumed that this patient has infectious mononucleosis with hepatitis and an associated anxiety state.

The answers are as follows: 1. A high level of iodine would have no effect on the situation. 2. Hypothyroidism usually is not associated with an anxiety state. The latter, however, is frequently associated with a low basal metabolism, and the condition is not alleviated by thyroid therapy. The administration of small doses of thyroid would quickly reveal whether any of the symptoms are due to hypothyroidism at present. 3. Patients convalescing from acute hepatitis, regardless of the etiology, not infrequently present the picture of an anxiety state. Results of liver function tests need not be abnormal at this stage of convalescence, but the liver is usually tender. Although this picture may be partly the result of a relatively prolonged illness, it is probably due to metabolic abnormalities resulting from liver dysfunction. 4. The elevated serum cholesterol level has no direct connection with anxiety but is due to either hypothyroidism, liver disease, or some other cause. 5. An elevated serum bilirubin level may be associated with depression but only indirectly with anxiety, insofar as it indicates the presence of inflammatory liver disease. In conclusion, it should be reemphasized that anxiety states are commonly associated with mononucleosis hepatitis and viral hepatitis.

THE MOAN TEST FOR AMEBIASIS

To the Editor:—*Since use of the complement-fixation test for amebiasis was discontinued by the U. S. Public Health Service there is a great need for a serologic test for this disease. What is the Moan test, and can the antigen be obtained commercially?*

H. B. Eisenstadt, M.D., Port Arthur, Texas.

Answer.—The need for a simple immunodiagnostic test to detect tissue invasion by Entamoeba histolytica has been voiced by many physicians. The first attempts to devise a diagnostic serologic test (complement-fixation test) for intestinal amebiasis were those of Izar, in 1914. During the last 46 years numerous methods of preparing antigens for the complement-fixation test and modifications of the technique of performing the test have been described and used by many investigators. The most that can be said for complement-fixation tests is that the results show greater consistency when there are extraintestinal lesions than they do in amebic colitis alone, and for this reason these techniques have not become acceptable routine diagnostic tools in the clinical laboratory.

Moan developed a new and rapid precipitin test procedure and reported (*Am. J. Trop. Med.* 6:499 [May] 1957) that the result of her test is frequently negative in patients with acute amebic dysentery, negative in 50% of persons classified as asymptomatic carriers, and positive in 85 to 100% of patients with clinical amebiasis and extraintestinal

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

amebiasis. Since the publication of Moan's paper her findings have not been fully confirmed by other investigators in the field. McHardy (*Gastroenterology* 30:535 [March] 1956) reported that he and Fry independently evaluated Moan's test on serum specimens from patients with known cases of acute and chronic amebic dysentery, on serum specimens from "carriers" of E. histolytica, and on specimens from patients with surgically proved cases of extraintestinal amebiasis and concluded that the test, in its present form, could not be relied on as a method for the diagnosis of amebiasis. Our preliminary experiences with Moan's test have substantiated McHardy's and Fry's conclusions.

Moan antigen is prepared and supplied by the Mobac Laboratories, 85 N. Lansdowne Ave., Lansdowne, Pa. The brochure accompanying the antigen currently supplied by the laboratory describes a different test procedure, the "Moan hemagglutination test for amebiasis," but fails to allude to the "Moan precipitin test." References about the usefulness of the new test procedure are not given and no publication describing its technique, specificity, and sensitivity has been seen.

CONSTITUENTS OF SEMEN AFTER VASECTOMY

To the Editor:—*What are the motile, variously shaped bodies seen in a seminal specimen collected from a patient after bilateral vasectomy and in which there are no live or dead spermatozoa?*

M.D., California.

Answer.—The prostatic secretion normally contains minute refractive granules, which are lecithin bodies. These bodies are small enough to display brownian movement. They are present in normal semen and assume greater prominence as the concentration of sperm is reduced. In seminal fluid free of spermatozoa, the lecithin bodies, which are ¼ to 1/10 of the size of a sperm head, may be the only formed elements that can be observed microscopically. Their movement can be easily distinguished from the movement of spermatozoa.

URETHRAL CATHETERIZATION

To the Editor:—*There seems to be a difference of opinion concerning the use of urethral catheters prior to operation on a pelvic organ. Some of the physicians in this area say that it is an outdated method and others say that it is not used at all. Would you comment on this subject?*

Clifford E. Payne, M.D., Lubbock, Texas.

Answer.—Urethral catheters are used at the time of operation for three reasons. First, they keep the bladder from filling with urine. This gives added exposure when working deep in the pelvis. Second, urethral catheters are used as a guide to identify the portion of the urethra when the surgeon is dissecting externally to the urogenital diaphragm, as in an abdominoperineal resection. Third, they are used to inject colored solutions into the bladder to help identify the bladder, when vaginal hysterectomy is done. The real question here is "Does the use of a urethral catheter make the operation safer or faster?" If it serves this purpose, it should be used. We should not be guided by "styles in operative procedures."

LEUKOPLAKIA VULVAE

To the Editor:—*Please outline the treatment of leukoplakia vulvae, since the available texts and literature give little information.*

William H. Kauffman, M.D., Willard, Ohio.

Answer.—Leukoplakia, wherever its location, represents a precancerous epithelial change. When it is located on the vulva, a biopsy should be performed to be certain that the diagnosis is correct, because lichen planus may simulate this lesion. When it is small, the lesion can be excised or electrocoagulated. Many physicians contend that a vulvectomy should be performed when the involved area is extensive. Some dermatologists treat leukōplakia of the skin with vitamin A, 100,000 units daily. This is long-term therapy. Some physicians feel that local application of an estrogen ointment may eradicate the lesion, but the effectiveness of this is seriously questioned by others. Surgical excision offers the only absolute, short-term treatment at present.

POLLEN ALLERGENS OF OREGON

To the Editor:—*A patient has been successfully desensitized to pollens prevalent in western Oregon but still has severe symptoms in late May and early June. He has received desensitization for four years, and pollen extracts of other allergens suspected of causing his discomfort have been added to his parent serum (western grasses and trees). He has not been retested in the past two years. Could you comment on this problem?*

Louis F. Michalek, M.D., Roseburg, Ore.

Answer.—The common offending pollens of the area about Roseburg, Ore., are outlined in the volume "Regional Allergy," edited by Samter and Durham (Springfield, Ill., Charles C Thomas, Publisher, 1955). Failure to obtain complete relief from desensitization with pollens can be due to a variety of factors, including (1) failure to include all offending pollens; (2) inadequate treatment; (3) excessive exposure to offending pollens; and (4) failure to respond to adequate desensitization injections.

The chief offending pollens in late May and early June, in that area of Oregon, belong to the family Graminiae (grasses). Frequently, patients who are excessively exposed during work or play develop symptoms in spite of intensive treatment, with the result that treatment with antihistaminics and other drugs is needed. Before presuming that desensitization cannot provide adequate comfort at the peak of the pollen season, the following suggestions are offered: (1) retest the patient with known offenders of that area; (2) determine if the patient's work or habits expose him excessively to the offending plants pollinating at that time; and (3) obtain information from the County Agent or the Department of Agriculture of Oregon State College at Corvallis, Ore., to determine if new crops have been introduced in that area. If all these possible causes have been eliminated, the patient may be advised that supplementary medication will be needed, in addition to his desensitization program, and that during the peak of the pollen season of late May and early June he might do well to avoid unnecessary exposure to the outdoor air, especially during the late afternoon and evening hours.

LOSS OF TASTE

To the Editor:—*A 62-year-old woman has had a change in her sense of taste, so that all foods taste bitter, resulting in a poor intake of food. About June, 1959, her lips and the left half of the tongue felt numb (as from a novocaine injection) and she had a burning sensation and sore spots on the tongue, followed, since November, 1959, by the bitter taste. The burning sensation becomes more pronounced about 5 p. m. and thereafter. She has been examined by an oral surgeon; an ear, nose, and throat specialist; and an internist. She was considered physically and mentally fit for her age. Vitamin B_{12} therapy was prescribed but has done no good. She has lost 12 lb. (5.4 kg.) in body weight, which disturbs her. She has monthly attacks of pain down the left leg and red spots (vesicles and pustules) on the left buttock. Repeated administration of smallpox vaccinations and estrogenic hormones have not caused a change. Two years ago, she suffered complete loss of hearing in the left ear, due to death of the 8th nerve, and a concurrent nystagmus when she is in the dark. What can be done for this patient?*

M.D., Illinois.

Answer.—This patient's variety of symptoms, in addition to the subjective change in the sense of taste, suggest the need for a detailed neurological examination. If there are supportive objective findings involving the cranial nerves, the possibility of an organic brain syndrome must be considered. Demonstrable sensory changes in the peripheral distribution of the left 5th, 7th, and 9th cranial nerves, along with the 8th-nerve deafness mentioned, would point to a localized lesion in the region of the left cerebellopontine angle. Any specific treatment of disagreeable taste will thus depend on a more complete search for the origin of the symptom complex described.

UNDESCENDED TESTIS

To the Editor:—*A 36-year-old man had a right inguinal herniorrhaphy performed 30 years ago. He claims that he has never felt his right testis in the scrotum or in the inguinal canal. The surgeon who repaired the hernia told the patient that during the operation the testis was found in the canal but that he was not able to bring it down to the scrotum. He also remembers giving the patient a course of hormone injections six months after the operation. At present the right testis cannot be found in either the scrotum or the canal. The patient, a physician, expresses concern over the possible development of a malignancy. Considering the lack of accurate records and the patient's concern and knowledge of the ensuing possibilities, I have advised him to have an exploratory operation. Do you agree?*

M.D., New York.

Answer.—If this patient is unduly concerned about the possibility of malignant changes in a testis and its presence or absence cannot be determined, an investigative operation of the inguinal and abdominal areas should be carried out. However, since only 12% of testicular tumors occur in undescended testes, surgical exploration can be delayed until such time as more definite indications exist.

SEROTONIN AND PSYCHIATRIC ILLNESSES

To the Editor:—*What is the relationship between psychopathology and an abnormal level of serotonin in the brain?*

M.D., New York.

Answer.—The relationship between serotonin concentrations in the central nervous system and human behavior remains obscure, despite several years of intensive research throughout the world. Victims of carcinoid tumors, who show very high levels of circulating serotonin, exhibit little in the way of psychopathology attributable to biochemical disturbance of the brain. This may be because serotonin passes the blood-brain barrier with difficulty. Monoamine oxidase inhibitors, such as iproniazid phosphate, used clinically as antidepressants, do raise the level of serotonin in the brain in animals. Reserpine, used as a depressant, releases serotonin from the brain in animals and man. Many hallucinogenic compounds, such as LSD-25, are antagonistic to serotonin in in vitro experiments. However, many *similar* substances are also antiserotonins but not hallucinogens. Reversal of the effects of reserpine by pretreatment with iproniazid has been advanced in favor of the importance of serotonin in brain function. Unfortunately, changes in serotonin levels are usually accompanied by changes in levels of norepinephrine and epinephrine and probably of other biogenic amines. The weight of the evidence suggests that serotonin does play a part in the economy of the central nervous system. The nature of this mechanism, its degree of importance, and its relation to psychopathological states are not known.

FACIAL INJURIES AND TRACHEOTOMY

To the Editor:—*Would you outline the indications for tracheotomy in accident victims who are in coma or who have had moderately severe or severe injury around the lower jaw and upper neck?*

James S. Reed, M.D., Lawrence, Kan.

Answer.—Tracheotomy should not be performed routinely for all patients who have moderate to severe injuries around the lower jaw and upper neck, because it is not always necessary. There is some inherent danger in tracheotomy, and it is too serious a procedure to be performed unless really needed. Some of the indications for tracheotomy include (1) facial and jaw injuries which preclude good oral hygiene and tracheal toilet; (2) airway obstruction when a satisfactory exchange cannot be maintained; (3) jaw and neck injury in most patients in whom coma has lasted more than 24 hours; and (4) crushing injuries of the chest in patients who require treatment with pressure-respiratory apparatus.

A tracheotomy should be performed when administration of an anesthetic is required in patients with these injuries and an anesthesiologist competent to use intratracheal tubes is not available. These injured patients have to be treated individually, and a good deal of common sense must be used. The liberal use of tracheotomy is advocated, but only when indicated and not as a routine procedure.

HEART BLOCK AND INSURANCE

To the Editor:—*What is the clinical significance of a right bundle-branch block? When it causes no symptoms and is without organic cause, what relevance does it have when a patient applies for life insurance?*

R. G. McCorkle, M.D., Austin, Texas.

Answer.—A large group of persons showing a complete right bundle-branch block, with no other evidence of cardiovascular disease, will have a mortality of 150 to 250%, depending on the relative number of young and old persons in the group. This signifies that the death rate will be one and one-half to two and one-half times the normally expected death rate.

This group will consist primarily of persons who have congenital blocks and post-toxic or infectious lesions and of those whose bundle-branch block is a manifestation of degenerative heart disease. The congenital lesions, in the absence of any other congenital defects, will have little significance from an underwriting standpoint. The toxic or infectious bundle-branch blocks will show the mortality of the underlying disease. Assuming that the patient is cured and there are no residual defects, these bundle-branch blocks will also have little significance. Most of the cases of bundle-branch block will be due to degenerative heart disease, and this disease will be the major cause of the increased mortality of the group as a whole.

Given a young person with a right bundle-branch block of unknown etiology, the chances that it is postinfectious, or congenital, are relatively great, and therefore only a small increase in mortality is to be expected. On the other hand, a right bundle-branch block discovered for the first time in the 5th or 6th decade of life probably is due to degenerative heart disease, and a mortality roughly double the normal is to be expected.

Each insurance company, however, acts in accord with its own experience and rules and the current opinion of its medical staff. Final appraisal would also depend on such related factors as family history, personal history, known duration of the block, stability of the lesion, age at which it developed or was discovered, and presence or absence of primary T wave changes.

INCREASED SKIN PIGMENTATION

To the Editor:—*A man with the native dark skin coloring of the Filipino people sought medical attention in May, 1959, for a papular rash on the skin of both his forearms. It was noted that he had been in contact with the chemical benzanthrone at work. The rash was treated conservatively, and the patient's condition was much improved until June, 1959, when he again came in contact with benzanthrone. The rash reappeared but had cleared by July, when the patient went on vacation. When he returned, his skin showed an intense discoloration, except for the area that had been covered by his bathing trunks during swimming and sunbathing. His skin had turned almost black in another two weeks. He is the only one of 200 men exposed to this chemical who has had a skin color change. What is the diagnosis?*

Francis A. Merlo, M.D., Elizabeth, N. J.

Answer.—The circumstances leading to the development of generalized hyperpigmentation of the exposed surfaces would appear to be related to the exposure to solar ultraviolet rays rather than to any concomitant exposure to a chemical. It would be necessary to ascertain whether this person had obtained the same degree of hyperpigmentation on previous exposures to a similar intensity and duration of sunlight. Anthracene and its derivatives can induce marked hyperpigmentation by increasing the responses of the skin to ultraviolet light, but this type of pigmentation would appear in a spotty distribution only where the material had been applied and could not induce a diffuse generalized hyperpigmentation.

READING OF ELECTROCARDIOGRAMS

To the Editor:—*What constitutes an adequate electrocardiographic interpretation? In a general hospital attending internists take turns (usually monthly) in reading the graphs recorded by physicians who have expressed no choice as to who is to perform this task. A qualified committee determines if new internists or physicians are qualified to read the graphs of their own patients. Would you comment on this?*

M.D., New York.

Answer.—The electrocardiogram is a graphic representation of the electrical forces of the heart, giving information concerning conduction, rate, rhythm, and myocardial status. It is not a substitute for a clinical evaluation, and it is best interpreted in the light of certain knowledge about the patient, such as previous medication, pertinent history, body habitus, age, sex, and blood pressure. The greatest value of the electrocardiogram can only be achieved if the full clinical record is available. This ideal circumstance often does not exist. Instead, one or several physicians have the responsibility, for a given hospital, of interpreting the electrocardiograms for the entire staff. This staff will vary from persons who are completely capable of interpreting their own electrocardiograms to those men who actually need a full cardiovascular consultative opinion and not just the interpretation of an electrocardiogram.

A competent cardiologist using the techniques of patience, common sense, missionary work, and judgment usually can give an adequate electrocardiographic interpretation. (Nothing is gained by arbitrary announcements that tracings will not be interpreted without adequate medical histories and physical examinations. Such threats only engender staff hostilities.) The interpretation should include a description of the electrocardiogram: rate, rhythm, conduction times, mean electrical axes, and abnormalities of contour or form. Such a description is not, however, the most important part of the interpretation, because for many physicians the description is only an indecipherable code. The final conclusion regarding the racing should consist of a possible etiological and physiological explanation of the abnormalities present. This last statement is made with the full appreciation that others in the field of electrocardiography have insisted that only an analysis of the electric pattern of the tracing is warranted and that any clinical extrapolation is an improper "overreading" of the tracing. I disagree. The electrocardiogram is a potent diagnostic tool, and the proper reading of a tracing should not only result in an "electric" interpretation of such factors as axis and time intervals, but express a physiological explanation for the changes. The electrocardiogram as we are discussing it here is a clinical instrument, and its full usefulness depends on a physician's ability to correlate a patient's history, physical findings, roentgenogram, and electrocardiogram.

The clinician who interprets electrocardiograms in the manner which I have described has a considerable responsibility. First, to extract from the electrocardiogram all the honest information it contains, and second, to be aware of the possible dangers of overreading those changes in the electrocardiogram which may have an equivocal significance. This is not easy, but a competent physician should be able to make the differentiation.

"LEFT VENTRICLE PARIETAL BLOCK"

To the Editor:—*What is a "left ventricle parietal block"?*

Andrew J. Brislen, M.D., Chicago, Ill.

Answer.—Parietal block and peri-infarction block involving the left ventricle are terms which have been used to describe a conduction disturbance characterized by QRS prolongation and having superficial similarity to bundle-branch block on the electrocardiogram. It is believed that the delay in conduction in these situations is due not to interruption of electrical flow through the main bundles but to disturbance in the spread of excitation in the area of myocardial injury, or necrosis related to myocardial infarction, so that the myocardial layers underlying the infarct are the last to receive excitation. The term parietal focal block was used by Alzamora-Castro and his associates in 1950, and peri-infarction block was a term used by First, Bayley, and Bedford in the same year.

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First, S. R.; Bayley, R. H.; and Bedford, D. R.: Peri-infarction Block; Electrocardiographic Abnormality Occasionally Resembling Bundle Branch Block and Local Ventricular Block of Other Types, Circulation **2**:31 (July) 1950.

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WASHINGTON NEWS

Committee Approves Health Bill . .
Social Security—Physicians . .
Aid for Medical Schools . .
Color Additives . .
Drug Probe . .
Miscellany . .

COMMITTEE APPROVES HEALTH BILL

After three months of closed-door work, the House Ways and Means Committee approved legislation that would set up a voluntary, federal-state program to finance health care for needy aged persons.

The measure, developed by committee chairman Wilbur Mills (D., Ark.), would cost an estimated 325 million dollars the first year, with the federal government paying 185 million dollars and the states paying 140 million. Total cost was expected to increase to 500 million dollars in five years.

Under the legislation, the states would have to provide roughly 50% of the funds, but they would not be required to participate. In addition, the states would determine the income or resource level of persons who could receive benefits, and provide any, or all, of a wide range of proposed benefits. The program would be similar to existing federal-state public assistance programs for the needy, but would cover only persons 65 years of age or older.

In approving the bill, the Ways and Means Committee rejected the controversial Forand bill that would establish a health plan under the social security system that would be financed through compulsory higher taxes on employers and employees, and the self-employed. This would cost an estimated 2 billion dollars or more.

Also rejected by the group was the administration's health proposal which would use the public assistance mechanism but cost considerably more than the Mills measure.

The committee's action was a defeat for organized labor which has been plugging hard for the Forand, social security measure. However, supporters of the scheme planned to renew their efforts in the Senate.

The bill was slated to go before the House Rules Committee, which is assigned the task of clearing legislation for action by the full House. Most Ways and Means Committee measures are brought up under a procedure barring amendments.

The following is the committee's brief description of the legislation:

Purpose.—The purpose is to initiate a new federal-state grant-in-aid program to help the states assist near-needy aged persons who need help in meeting their medical expenses. Participation will be at the option of each individual state and will only be effective after June, 1961, upon the submittal of a plan which would meet the general requirements specified in the bill.

Eligibility.—Persons to be eligible are those 65 years of age, whose income and resources—taking into account their other living requirements as determined by a state—are insufficient to meet the cost of their medical services. Persons eligible for payments under this program are not eligible under the other federal-state public assistance programs.

Scope of Benefits.—The scope of benefits provided will be determined by the states. The federal government, however, will participate under the matching formula in any program which provides any or all of the following services up to the limits specified: (a) inpatient hospital services up to 120 days per year; (b) skilled nursing-home services; (c) physicians services; (d) outpatient hospital services; (e) organized home care services; (f) private duty nursing services; (g) therapeutic services; (h) major dental treatment; (i) laboratory and x-ray services up to $200 per year; and (j) prescribed drugs, up to 200 dollars per year.

Federal Matching.—The federal government will provide funds in accordance with an equalization formula under which the federal share will be between 50 and 65% of the costs, depending upon the per capita income of the state. A program cannot be more liberal than a medical program under a state's old-age assistance program, and there can be no reduction in existing public assistance programs to finance the new program.

Cost and Number of Persons Affected.—An estimated 500,000 to 1 million persons aged 65 years and over who will be ill during a year. State plans could provide potential protection to as many as 10 million persons whose financial resources are such that if they have extensive medical expenses, they could qualify.

SOCIAL SECURITY–PHYSICIANS

Despite the opposition of the American Medical Association, the House Ways and Means Committee voted to include self-employed physicians under the Social Security System.

Coverage also would be extended to medical and dental interns. An estimated 150,000 self-employed physicians would be affected under the measure, and would be required to pay 4½% social security tax effective for taxable years ending on or after Dec. 31, 1960.

The measure, part of an overall bill amending the social security system, was slated to go to the full

House and then the Senate. Other provisions, in addition to one for health care of needy elderly persons, included elimination of the requirement that persons be 50 years of age for eligibility under the social security program for the permanently and totally disabled.

AID FOR MEDICAL SCHOOLS

The American Medical Association notified Congress that it supports a temporary program of federal-state aid for the construction and expansion of medical schools "where maximum freedom of the school from federal control is assured."

"We believe . . . that there is sufficient need for assistance in the expansion, construction, and remodeling of the physical facilities of medical schools to justify a one-time expenditure of federal funds, on a matching basis (by the states)," said Dr. F. J. L. Blasingame, A. M. A. Executive Vice-president, in a letter to a House commerce subcommittee headed by Rep. Kenneth A. Roberts (D., Ala.).

The subcommittee was informed of the A. M. A. stand as it opened hearings on proposals for aid to medical schools, grants for medical research, and for federal medical and dental scholarships. The A. M. A. took no position on the latter two proposals, which are still under consideration by A. M. A. committees.

In the letter to the subcommittee, Dr. Blasingame noted that in general the Association is opposed to federal aid in those areas where private citizens and local and state governments are capable of providing for themselves "because of the degree of control and regulation which must necessarily accompany federal funds."

"The Association strongly believes that in establishing and maintaining high standards of medical education continued attention must be given to the adequacy of physical facilities, the availability of qualified instructors and the availability of teaching material and patients for the clinical phases of medical education," the letter stated. "These factors place definite limitations on the number of medical students who can be adequately educated. Any attempt to increase the number of students without regard to these conditions will result in a lowering of the standard of medical education. In turn, increased numbers of inadequately trained physicians will serve only to destroy the high standard of medical care which has been developed in this country."

Dr. Blasingame urged the subcommittee to eliminate a provision that might "needlessly establish a precedent for urging or inducing medical schools to increase their enrollment more rapidly than is justified by their facilities, personnel and teaching material."

Chief measure before the subcommittee calls for a five-year, 250 million dollar program of grants for the improvement of existing schools; and a ten-year, 100 million dollar program for construction of new schools.

The administration submitted its own proposal in the field—a five-year, 100 million dollar plan for aid to medical and dental schools.

COLOR ADDITIVES

The House Commerce Committee approved the administration's bill to allow minute quantities of some coal-tar dyes in food, drugs, and cosmetics for coloring, even though large amounts may be harmful to human beings.

However, the bill would continue the flat ban on coal-tar dyes found to produce cancer in test animals or human beings.

At present, the government is required under law to prohibit use of any coal-tar dye colorings even though the amount used in the product is so tiny that no possible danger to human beings could be present. The measure would allow the government to establish "tolerances" for use of these dyes.

The administration has contended that little is known about possible chemical causes of cancer and therefore no "tolerances" should be granted for cancer-producing agents until scientific knowledge is more exact.

DRUG PROBE

Secretary Arthur S. Flemming of the Department of Health, Education and Welfare told Congress he will appoint a panel of outside scientists to review Food and Drug Administration policies on approving new drugs.

In testimony before the Senate antitrust subcommittee, Dr. Barbara Moulton, a former FDA medical officer, accused the agency of lax enforcement of drug safety laws. Denying the charge later, FDA Commissioner George P. Larrick declared FDA decisions "have been supported by adequate science and sound medical judgment."

Flemming disputed one of Dr. Moulton's specific charges—that folic acid had been approved as a safe food additive. Actually, he said, the acid had been kept off the safe list in line with Dr. Moulton's own recommendations.

Flemming told the subcommittee the FDA will closely check advertising matter sent to physicians for possible misleading claims. If any such claims are uncovered and not corrected within a specified time, the drug will be ordered off the market, he said.

MISCELLANY

A Senate aviation subcommittee opened hearings on Federal Aviation Agency safety rules. The Air Line Pilots Association criticized a mandatory aged 60 retirement for commercial pilots, and the Aircraft Owners and Pilots Association criticized a requirement that only specially-designated physicians could perform qualifying physical examinations for private pilots.

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The usual adult dosage is 15 mg. with meals and 30 mg. at bedtime. For severe manifestations 30 mg. or more four times daily may be prescribed. Pro-Banthīne (brand of propantheline bromide) is supplied as sugar-coated tablets of 15 mg.

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1. Henrickson, W. E.: The Generalist Looks at Constipation, GP 18:128 (Oct.) 1958.
2. Bercovitz, Z. T.: *Medical Forum: Should Colectomy and Permanent Ileostomy Be Considered for Children with Ulcerative Colitis,* Mod. Med. 25:18 (July 1) 1957.
3. Lumsden, K., and Truelove, S. C.: *Intravenous Pro-Banthīne in Diagnostic Radiology of the Gastrointestinal Tract, with Special Reference to Colonic Disease,* Brit. J. Radiol. 32:517 (Aug.) 1959.

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MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.

1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 1.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-30.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 26-29.

AMERICAN

1960

June

American Physical Therapy Association, Penn-Sheraton Hotel, Pittsburgh, June 26-July 2. Miss *Lucy Blair, 1790 Broadway, New York 19*, Acting Executive Director.

Idaho State Medical Association, Sun Valley, June 15-18. Mr. Armand L. Bird, Sonna Bldg., Boise, Idaho, Executive Secretary.

Maine Medical Association, Hotel Samoset, Rockland, June 19-21. Dr. Daniel F. Hanley, P. O. Box 240, Brunswick, Maine, Executive *Director.*

Northwest Proctologic Society, Roche Harbor, San Juan Island, Wash., June 21-24. *Dr. L. D. Leslie*, 1162 Willamette St., Eugene, Ore., Secretary-Treasurer.

Society of Nuclear Medicine, Estes Park, Colo., June 22-25. Dr. Thad P. Sears, Veterans Administration Hospital, Denver 20, Chairman.

July

American Goiter Association, Church House, London, England, July 5-8. Dr. John C. McClintock, 702 Madison Ave., Albany 8, N. Y., Secretary.

American Society of Facial Plastic Surgery, *Hotel Elysee, New York* City, July 22. Dr. Samuel M. Bloom, 123 E. 83d St., New York 28, Secretary.

Flying Physicians Association Hawaii Cruise, leaving Los Angeles and San Francisco, July 11. For information write: Mr. Mark E. DeGroff, P. O. Box 3275, Tulsa, Okla.

Oregon Cancer Conference (Second Annual), Sheraton Hotel, Portland, July 7-8. Dr. Martin A. Howard, 115 S. W. Taylor St., Portland 5, Ore., Chairman.

Rocky Mountain Cancer Conference, Hilton Hotel, Denver, July 20-21. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary, Colorado State Medical Society.

August

American Association of Blood Banks, Jack Tar Hotel, San Francisco, Aug. 21-26. For information write: AABB Central Office, Suite 1619, 30 N. Michigan, Chicago 2.

American Congress of Physical Medicine and Rehabilitation, Mayflower Hotel, Washington, D. C., Aug. 21-26. Mrs. Dorothea C. Augustin, 30 N. Michigan Ave, Chicago 2, Executive Secretary.

American Hospital Association, Civic Auditorium, San Francisco, Aug. 27-Sept. 1. Mr. Maurice J. Norby, 840 N. Lake Shore Dr., Chicago 11, Secretary.

American Institute of Ultrasonics in Medicine, Statler-Hilton Hotel, Washington, D. C., Aug. 20. Dr. Dorothy M. Stillwell, Dept. of Phys. Med. and Rehab., Univ. of Colorado Med. Center, Denver 20, Chairman.

American Physiological Society, Stanford University, Calif., Aug. 22-26. Mr. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

American Society of Clinical Hypnosis, Miami, Fla., Aug. 7-10. Dr. Seymour Hershman, 6770 N. Lincoln Ave., Chicago 46, Secretary.

American Society for Pharmacology and Experimental Therapeutics, University of Washington, Seattle, Aug. 21-25. Dr. Karl H. Beyer, Merck Sharp & Dohme Research Laboratories, West Point, Pa., Secretary.

American Veterinary Medical Association, Denver-Hilton Hotel, Denver, Aug. 15-18. H. E. Kingman Jr., 600 S. Michigan Avenue, Chicago 5, Executive Secretary.

Biological Photographic Association, Inc., Utah Motor Lodge, Salt Lake City, Utah, Aug. 23-26. Miss Jane H. Waters, Box 1668, Grand Central P. O., New York 17, Executive Secretary.

Conference on the Chemical Organization of Cells: Normal and Abnormal, University of Wisconsin, Madison, Aug. 25-27. Dr. J. F. A. McManus, Dept. of Pathology, University of Alabama Medical Center, Birmingham, Chairman.

Gerontological Society, Inc., Mark Hopkins Hotel, San Francisco, Aug. 7-12. Mrs. Marjorie Adler, 660 S. Kingshighway Blvd., St. Louis 10, Administrative Secretary.

National Medical Association, Inc., Penn-Sheraton Hotel, Pittsburgh, Aug. 8-11. Dr. John T. Givens, 1108 Church St., Norfolk, Va., Executive Secretary.

Reno Surgical Society, Mapes Hotel, Reno, Nev, Aug. 18-20. Dr. Gilbert G. Lenz, 505 S. Arlington Ave., Reno, Nevada.

Rocky Mountain Radiological Society, Denver-Hilton Hotel, Denver, Aug. 11-13. Dr. John H. Freed, 4200 E. 9th Ave., Denver 20, Secretary-Treasurer.

St. Joseph's Hospital Annual Clinics, St. Joseph's Hospital, Denver, Aug. 3-5. Dr. W. H. Leitch, St. Joseph's Hospital, 1818 Humboldt St., Denver 18, Chairman.

West Virginia State Medical Association, The Greenbrier, White Sulphur Springs, Aug. 25-27. Mr. Charles Lively, Box 1031, Charleston 24, W. Va., Executive Secretary.

September

American Academy of Pediatrics, and American Academy of General Practice, Louisiana Chapter, Roosevelt Hotel, New Orleans, Sept. 23. Dr. Herbert B. Rothschild, 1520 Louisiana Ave., New Orleans 15, Chairman of Publicity Committee.

American Medical Writers' Association, Hotel Morrison, Chicago, Sept. 30-Oct. 1. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

American Roentgen Ray Society, Ambassador Hotel, Atlantic City, Sept. 27-30. Mr. Hugh Jones, 20 N. Wacker Dr., Chicago 6, Director, Public Relations.

American Society of Clinical Pathologists, Palmer House, Chicago, Sept. 24-Oct. 2. Mr. Claude E. Wells, 445 Lake Shore Drive, Chicago 11, Executive Secretary.

College of American Pathologists, Palmer House, Chicago, Sept. 24-27. Dr. Arthur H. Dearing, 2115 Prudential Plaza, Chicago, Executive Director.

Colorado State Medical Society, Stanley Hotel, Estes Park, Sept. 14-17. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary.

Delaware, Medical Society of, Rehoboth, Del., Sept. Mr. Lawrence C. Morris Jr., 1925 Lovering Ave., Wilmington 6, Del., Executive *Secretary.*

Flying Physicians Association, third clinical meeting, Western Hills Lodge, Wagoner, Okla., Sept. 6-9. For information write: Flying Physicians Association National Headquarters, P. O. Box 3275, Tulsa, Okla.

Inter-Society Cytology Council, Palmer House, Chicago, Sept. 23-25. Dr. Paul A. Younge, 1101 Beacon St., Brookline 46, Mass., Secretary.

Kentucky State Medical Association, Louisville, Sept. 20-22. Mr. J. P. Sanford, 1169 Eastern Parkway, Louisville 17, Ky., Executive Secretary.

Maryland, Medical and Chirurgical Faculty of the State of, Semiannual Meeting, Ocean City, Sept. 16. Mr. John Sargeant, 1211 Cathedral St., Baltimore 1, Executive Secretary.

Michigan State Medical Society, Detroit, week of Sept. 25. Dr. D. Bruce Wiley, 606 Townsend St., Lansing 15, Mich., Secretary.

Montana Medical Association, Baxter Hotel, Bozeman, Sept. 15-17. Dr. William E. Harris, 114 N. Second, Livingston, Montana, Secretary.

National Cancer Conference, American Cancer Society, Inc., and the National Cancer Institute, Minneapolis, Minnesota, Sept. 13-15. Dr. Roald M. Grant, 521 W. 57th St., New York 19, Coordinator.

National Recreation Congress, Shoreham Hotel, Washington, D. C. Sept. 25-29. Willard B. Stone, 8 W. Eighth St., New York 11, Secretary.

Nevada State Medical Association, Stardust Hotel, Las Vegas, Sept. 7-10. Mr. Nelson B. Neff, P. O. Box 2790, Reno, Nev., Executive Secretary.

New England Society of Anesthesiologists, Bretton Woods, N. H., Sept. 18-19. Dr. Thomas K. Burnap, P. O. Box 81, Kenmore Station P. O., Boston 15.

Oregon State Medical Society, Portland, Sept. 7-9. Mr. Roscoe K. Miller, 2164 S. W. Park Place, Portland 5, Ore., Executive Secretary.

Pacific Dermatologic Association, Empress Hotel, Victoria, British Columbia, Canada, Sept. 1-4. Dr. Edward J. Ringrose, 2636 Telegraph Ave., Berkeley 4, Calif., Secretary-Treasurer.

Society for Pediatric Radiology, Ambassador Hotel, Atlantic City, N. J., Sept. 26. Dr. Richard G. Lester, 412 Union St., S. E., Minneapolis 14, Minn., Secretary-Treasurer.

Southern Trudeau Society (and Southern Tuberculosis Conference), Hotel Francis Marion, Charleston, S. C., Sept. 14-16. Mr. Judson M. Allred Jr., P. O. Box 9865, Northside Station, Jackson, Miss., Secretary-Treasurer.

Tennessee Valley Medical Assembly, Read House, Chattanooga, Tenn., Sept. 26-27. Dr. Robert A. Waters, 109 Medical Arts Bldg., Chattanooga, Chairman.

Tri-State Medical Assembly, Captain Shreve Hotel, Shreveport, La., Sept. 14-15. Dr. J. W. Wilson Jr., 940 Margaret Place, Shreveport, La., Secretary-Treasurer.

Utah State Medical Association, Hotel Utah Motor Lodge, Salt Lake City, Sept. 20-23. Mr. Harold Bowman, 42 S. 5th East, Salt Lake City 2, Executive Secretary.

(Continued on page 34)

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COMPARISON OF CHLOROTHIAZIDE AND MERALLURIDE

NEW RAPID METHOD FOR QUANTITATIVE EVALUATION OF DIURETICS IN BED-PATIENTS IN CONGESTIVE HEART FAILURE

Harry Gold, M.D., Nathaniel T. Kwit, M.D., Charles R. Messeloff, M.D., Milton L. Kramer, M.D.,
Argyrios J. Golfins, M.D., Theodore H. Greiner, M.D., Elizabeth A. Goessel, M.A., John H. Hughes, A.B.
and
Leon Warshaw, M.D., New York

A new method for ascertaining diuretic efficacy, carried out in bed-patients in congestive failure within the framework of a highly effective therapeutic regimen which included rest, digitalization, and salt restriction, was applied in a comparison of the maximally effective doses of chlorothiazide and meralluride, a 2-Gm. oral dose of the former and a 2-cc. intramuscular dose of the latter. Each patient received both agents, but not simultaneously, the sequence alternating within and between patients. The comparisons were made in terms of 24-hour weight losses. Only the first four doses with paired responses provided the data which were analyzed by signs and the sign test, also by ratios with confidence limits. Contrary to the prevailing opinion, the 2-Gm. oral dose of chlorothiazide was found to exert only 40% of the diuretic effect of the 2-cc. intramuscular dose of meralluride.

IN a recent report we described a method for the quantitative comparison of diuretic agents in bed-patients in congestive heart failure, which, with respect to efficacy in clearing edema, yields reliable answers, subject to verification by standard statistical tests, with a relatively small number of patients, in a period of several days. We are now applying this method to the evaluation of several older and newer diuretics. A comparison of the currently popular chlorothiazide (Diuril) with a representative organic mercurial, meralluride (Mercuhydrin) sodium, is the subject of the present report. A preliminary report[1] of the results was presented at the autumn, 1959, meeting of the American Society for Pharmacology and Experimental Therapeutics.

Method

For a complete account of the method, the reader may refer to our previous reports.[2] We relate here only the salient features of it. The assay is carried out with bed-patients in congestive failure, and the pertinent data emerge out of a highly effective regimen of therapy along the general lines described in an earlier study.[3] The diet is fairly

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From the Department of Pharmacology, Cornell University Medical College; the Hospital for Joint Diseases; the Cardiovascular Research Unit of the Beth Israel Hospital; and the Lincoln Hospital. Dr. Golfinos is a Postdoctoral Fellow, U. S. Public Health Service. Dr. Greiner is now at Baylor University College of Medicine, Houston, Texas.

constant, salt-restricted, and liberal in the supply of fluids. Digitalization is maintained in a conventional manner. The patient is weighed accurately on a scale sensitive to 0.25 lb. (0.11 kg.) every morning, under conditions that are constant with respect to obvious factors that may influence the weight in this range. A diuretic agent is given daily or every other day. Two agents are used concurrently, one the "test drug" and the other the "standard" for comparison. At present we are using the organic mercurial meralluride, administered by intramuscular injection, as the "standard." The doses are at the maximally effective levels for the respective drugs (average and approximate "ceiling doses"), which may be established by dose-response curves or less formal preliminary testing. In a series of doses, the two drugs are given in the patterns ABBA and BAAB, and the two patterns alternate in the group of patients in the assay. This eliminates a source of bias that is possible when one drug always precedes or follows the other in paired response comparisons. The response is the weight loss 24 hours after the dose in each case. We believe that this measure, being a comprehensive expression of the action in clearing edema, may be a more stable and reliable index than the excretion of a urinary constituent such as sodium for the comparison of the diuretic efficacy of agents which may differ in their actions with respect to urinary electrolytes.

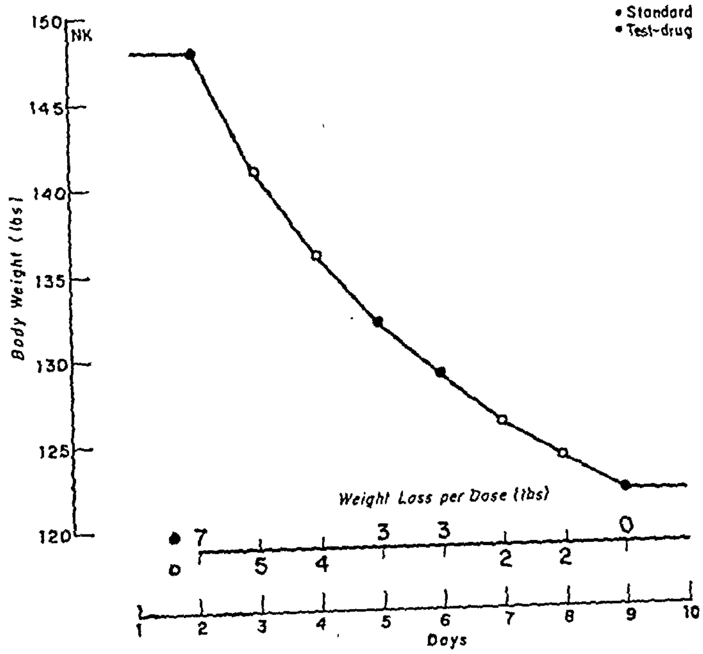

Fig. 1 (case 5 in table 1).—Man, aged 55 years, with rheumatic heart disease, mitral stenosis and insufficiency, adherent pericardium, enlarged heart, auricular fibrillation, and far-advanced congestive failure, with massive ascites, treated with diet of milk and water, 1.5 liters of each, daily maintenance dose of 0.2 mg. of digitoxin, and daily intramuscular dose of 2 cc. of meralluride. Patient lost one-third of initial body weight. Standard and test drug are both 2 cc. of meralluride. Doses of diuretic were given at points on curve and numbers below show corresponding 24-hour weight losses.

Figure 1 illustrates the kind of responses produced by a series of daily intramuscular doses of 2 cc. of meralluride in a test patient. There was a fairly regular succession of 24-hour weight losses corresponding to the doses. The ABBA pattern applied to them yielded a series of paired responses of a "standard" (A) and "test drug" (B). Comparison of the two drugs, expressed as the ratio T/S, yielded for the first two pair the value 90 and for the first four pair the value 100, a close agreement with the expected value. This might be anticipated, since both A and B were the same drug. In our previous study[2] such uniformity tests made with the averages for groups of patients also showed good agreement. The closest agreement was obtained in a group of 13 patients, with use of two paired response comparisons in each patient and 2 cc. of meralluride for all the doses (table 1). The average T/S turned out to be 100.7, with confidence limits of 88.8 and 112.6, the expected value being 100. In a further challenge of the method with 2 cc. of meralluride as the "standard" against 1 cc. of meralluride as the "test drug," the latter produced nearly two-thirds (T/S 61.6) of the effect of the former, a value in line with that obtained by our previous method of assay in ambulant patients in congestive failure, with use of the dose-response curve.[4]

Table 1.—*Bioassay of Meralluride in Bed-Patients in Congestive Failure**

Case No.	Pattern	Total Edema, Lb.	Total Weight Loss for 2 Doses, Lb. Standard (S)	Test Drug (T)	Efficacy of Test Drug % (T/S)
1..............	ABBA	13 5	5.25	5.25	100.0
2..............	BAAB	22.0	9.5	9.5	100.0
3..............	ABBA	27.0	6.5	4.5	69.2
4..............	BAAB	26.7	6.6	8.2	124.2
5..............	ABBA	43.0	10.0	9.0	90.0
6..............	BAAB	15.0	6.0	6.0	100.0
7..............	ABBA	33.0	8.0	8.0	100.0
8..............	BAAB	60.0	9.0	9.0	100.0
9..............	ABBA	21.5	7.0	6.5	92.9
10..............	BAAB	22.0	3.5	3.0	85.7
11..............	ABBA	22.5	5.0	5.5	110.0
12..............	BAAB	16.25	6.0	9.0	150.0
13..............	ABBA	8.9	3.8	3.3	86.8
Average.....					100.7†

* "Standard" and "test drug" both 2 cc. of meralluride I.M.
† Confidence limits at 5%: 88.8 and 112.6.

The ratios of the measured responses, expressed for a group of test patients as the average with confidence limits, as described above, is one form of analysis of the data. The paired comparisons may also be analyzed on the basis of signs with the sign test for reliability of the answer. This does not show the magnitude of a difference between two compounds, only the direction of the difference. It shows only which of the compounds is the more effective one. The analysis by signs has the advantage of making more data available, namely, responses obtained under conditions unsuited for the ratio method, and the further advantage of great simplicity in calculation, as will be seen presently.

A word about the kind of information yielded by this method of assay. It is customary to suppose that a compound which is more potent than another is also more effective, as is, for example, the case with the currently popular chlorothiazide and hydrochlorothiazide. This is a common error, since with such information alone all one needs to do to secure a similar effect with the weaker material is to give a larger dose. Higher potency has therapeutic importance only if there are facts to show that the larger dose of the weaker compound is for some reason unfavorable or precluded, as by higher toxicity or inconvenience of administration. Our method of assay does not show how much of each drug is needed to produce similar effects. It does not, therefore, provide an expression of relative "potency," in the sense of the conventional use of the term in pharmacology. Since the comparisons are made here in terms of the maximum effects each drug can produce in a particular patient, irrespective of the dose, the results show which of the two has the greater potentiality for clearing edema. Accordingly, we avoid the term relative "potency" and employ in its place the term relative "efficacy" for emphasis on the particular kind of information about a diuretic which is supplied in a comparison by this method. Since the period for the response, namely, 24 hours after the dose, is constant for the two drugs, an inversion of the T/S ratio, S/T, yields information on the difference in the time it would take to clear the edema by each of the drugs if each alone were used in its maximally effective dose.

Chlorothiazide Versus Meralluride

A series of 22 patients was involved in this study. Their characteristics are summarized in table 2. The approximate "ceiling" dose of meralluride was taken as 2 cc. by intramuscular injection on the basis of a dose-response curve previously reported.[4] The dose of chlorothiazide was 2 Gm., orally administered on an empty stomach, on the basis of the consensus of reports in the literature that larger amounts produce no greater response.[5] Totals of 136 doses of each drug were given.

Table 2.–*Characteristics of Patients with Congestive Heart Failure in Study*

No.	Sex	Age, Yr.	Weight, Lb	Edema, Lb.*	Diagnosis
1	F	72	218.5	7.0	Hypertension, enlarged heart, regular sinus rhythm, hepatic cirrhosis
2	F	68	136.0	10.5	Arteriosclerosis, enlarged heart, regular sinus rhythm
3	F	63	124.0	7.5	Arteriosclerosis, enlarged heart, regular sinus rhythm
4	M	48	132.5	23.0	Arteriosclerosis, syphilis, coronary thrombosis, enlarged heart, regular sinus rhythm
5	F	67	147.5	7.5	Arteriosclerosis, enlarged heart, regular sinus rhythm
6	F	57	148.0	19.0	Arteriosclerosis, enlarged heart, regular sinus rhythm, diabetes
7	F	70	159.5	7.0	Arteriosclerosis, hypertension, enlarged heart, regular sinus rhythm
8	M	48	232.0	40.0	Hepatic cirrhosis with anasarca and ascites, obesity
9	M	71	188.0	30.0	Arteriosclerosis, enlarged heart, regular sinus rhythm, diabetes
10	M	67	182.5	20.0	Arteriosclerosis, syphilis, enlarged heart, regular sinus rhythm, hepatic cirrhosis
11	F	71	106.0	12.0	Arteriosclerosis, enlarged heart, regular sinus rhythm
12	M	61	146.5	20.0	Bronchial asthma, cor pulmonale, enlarged heart, regular sinus rhythm
13	M	68	217.0	45.5	Arteriosclerosis, enlarged heart, auricular fibrillation, obesity
14	M	73	138.5	10.0	Arteriosclerosis, pulmonary emphysema, cor pulmonale, enlarged heart, regular sinus rhythm
15	F	39	244.0	17.0	Unknown, traumatic pericarditis, enlarged heart, regular sinus rhythm, obesity
16	F	70	124.0	3.0	Hypertension, enlarged heart, regular sinus rhythm
17	F	63	196.5	4.5	Hypertension, enlarged heart, regular sinus rhythm, obesity
18	M	59	168.0	4.0	Arteriosclerosis, enlarged heart, regular sinus rhythm
19	M	75	162.0	15.0	Arteriosclerosis, enlarged heart, auricular flutter
20	M	73	123.5	4.5	Arteriosclerosis, hypertension, syphilis, enlarged heart, auricular fibrillation
21	M	70	151.5	6.0	Arteriosclerosis, syphilis, enlarged heart, aortic insufficiency, regular sinus rhythm
22	M	64	180.25	6.0	Arteriosclerosis, hypertension, enlarged heart, regular sinus rhythm

* Determined by difference between initial weight and edema-free weight at end of treatment.

Fourteen of these patients fulfilled the qualifications established in the previous study for a supply of data suitable for computation of efficacy in terms of ratios. In figures 2 and 3 are charted the data from two cases which are fairly typical of the course of events in an assay. The values for ratios are taken from the steep portion of the falling weight curve, usually the responses to the first four doses. In two pair the responses to the two doses of the "standard" (A) are added, similarly for the "test drug" (B), and the ratio of their sums or averages per dose (T/S) is taken as the efficacy of the test drug in terms of the standard. In the case of figure 2, the 2-Gm. oral dose of chlorothiazide showed a diuretic effect 57.1%, and in the case of figure 3, an effect 87.5%, of that of the 2-cc. intramuscular dose of meralluride.

Table 3 summarizes the results of the assay with these 14 patients. In the first seven patients the drugs were given daily, and in the remaining seven every other day. The alternating patterns were used in all but one, patient 13, who was tested before the new design was adopted. It may be seen that the values for relative effectiveness of the two drugs differ widely in different patients, the chlorothiazide showing a diuretic effect all the way from 0 to 87.5% of that of meralluride, the average for the group being 39.7%. Different groups of patients may be expected to give different answers, but the confidence limits show that in 95 of 100 assays such as this, the answers would fall somewhere between 26.3 and 53.1%.

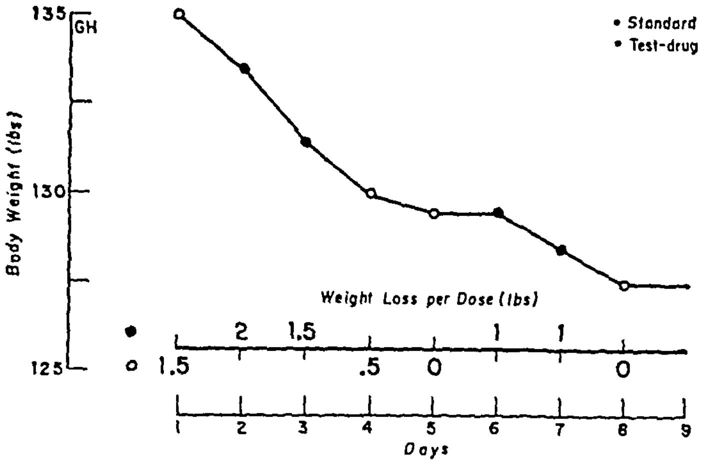

Fig. 2 (case 2 in tables 2 and 3).—Woman, aged 68 years, with arteriosclerotic heart disease, enlarged heart, sinus rhythm, and moderate congestive failure, treated with low-salt diet, free water intake, and daily dose of diuretic. Standard was 2 cc. of intramuscularly given meralluride and test drug 2 Gm. of orally given chlorothiazide. Doses of diuretic were given at points on curve and numbers below show corresponding 24-hour weight losses.

Since the weight losses assigned to each drug include the effect of the base-line regimen (rest in bed, salt restriction, and digitalization), we have obtained some information on how it might influence the results of an assay, from the weight changes in the drug-free days. In the case of two other diuretics,[2] adjustment for the drug-free day reduced the efficacy value of the test drug from 51.5 to 36.1% in one assay and from 59.5 to 44.9% in the other.

In the case of the chlorothiazide assay, the seven patients (8 to 14, inclusive, of table 3) with the drug-free day yielded the value 32.4% of that of meralluride (confidence limits of 10.6 and 54.2 at the 5% level), which fell to 20.7% when adjusted for the weight change in the drug-free days. The collective experience with the drug-free day up to the present indicates that the unadjusted estimate of efficacy is somewhat biased in favor of the weaker of the two drugs.

This position of chlorothiazide in relation to meralluride, on the basis of ratios, received strong support from the analysis of the data on the basis of signs. We use the formula $\frac{(X-Y-1)^2}{X+Y}$. Arbitrarily we assign a (+) to a patient or a pair of doses when the standard is more effective and a (−) when the test drug is more effective. We add up the numbers of each sign. We substitute for X in the formula the larger of the two sums and for Y, the smaller sum, subtract 1 as a "correction" factor,[6] square the result, and divide by X+Y. When the resulting number exceeds 3.84 it means that an observed difference between two drugs is probably not accidental and may be expected to appear in 95 or more of 100 repetitions of the experiment. How it was done in this experiment may help to emphasize the simplicity of the sign test for assuring the validity of an observed difference between drugs. In the present assay, we have 14 patients, each with a chance to "choose" between the two drugs. We also have 30 paired comparisons or 30 chances for these 14 patients to "choose" between them in the form of weight losses per dose. Of the 14 patients in whom only the first two pair or four doses (one case with four pair) were used for comparisons, 13 "favored" meralluride, none "favored" chlorothiazide, and one patient could not distinguish them. The formula $\frac{(13-0-1)^2}{13+0}$ yielded the highly significant sign test result of 11.08. Of the 30 pairs, 27 "favored" meralluride, 2 "favored" chlorothiazide, and 1

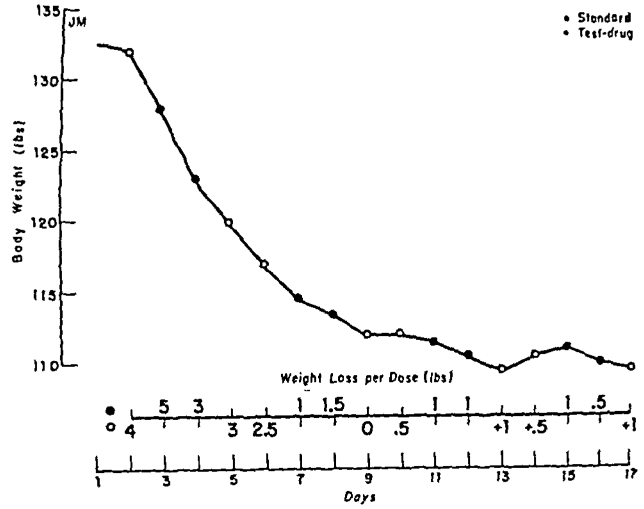

Fig. 3 (case 4 in tables 2 and 3).—Man, aged 48 years, with arteriosclerotic and syphilitic heart disease, coronary thrombosis, enlarged heart, sinus rhythm, and advanced congestive failure, treated with low-salt diet, free water intake, daily maintenance dose of 0.1 mg. of digitoxin, and daily dose of diuretic. Standard was 2 cc. of intramuscularly given meralluride and test drug 2 Gm. of orally given chlorothiazide. Doses of diuretic were given at points on curve and numbers below show corresponding 24-hour weight losses.

could not distinguish. The formula $\frac{(27-2-1)^2}{27+2}$ yielded the highly significant sign test result of 19.9.

Further confirmation was obtained from the results in all 22 patients (table 2), making use of all the paired doses they received. They supplied 136 paired comparisons. In terms of patients there were no reversals; all 22 "favored" meralluride; sign test result, 20.04. Among the 136 pairs there were some reversals; meralluride was more effective in 111 pairs; chlorothiazide was more effective in 14 pairs; the two drugs were equal in 11 pairs; the sign test result was 73.7.

From the sign test values, therefore, there remains little doubt that meralluride is a more effective diuretic than chlorothiazide, and from the ratios of the measured responses which show the magnitude of the difference, the 2-Gm. oral dose of chlorothiazide produces an effect about 40% of that of the 2-cc. intramuscular dose of meralluride.

The result of an assay by the same method in our previous study,[2] in which the 1 cc. of meralluride produced about 60% of the effect of 2 cc., makes it possible to define the efficacy of chlorothiazide more closely by the ratio 40:60, which leaves for the 2-Gm. oral dose of chlorothiazide a diuretic effect of about 70% of that of 1 cc. of meralluride given intramuscularly.

We present here a few additional observations which were made possible by one patient with two hospitalizations for advanced congestive heart failure with 45 and 50 lb. of edema, respectively, and in clinically indistinguishable states. In the first admission, there was a "casual clinical trial" of chlorothiazide. He was placed in bed, on a salt-restricted diet (2 Gm. of salt per day), continued digitalization, and a 2-Gm. oral dose of chlorothiazide daily. The patient's course is charted in figure 4. He began to lose weight promptly and continued to do so at an average rate of 2.35 lb. (1.08 kg.) per day in the first 10 days, losing in all 39 lb. (17.7 kg.) in 22 days. This produced a favorable impression toward chlorothiazide. It was not then clear how to interpret the fact that response to it ended when 11 lb. (5 kg.) of edema still remained. This was cleared by administration of a daily 2-cc. intramuscular dose of meralluride. It is customary to ascribe such a result to the development of "tolerance" to a diuretic, although acquired "tolerance" to chlorothiazide has been denied.[7]

The second hospitalization and the formal assay supplied some explanations. The treatment on this admission was the same except that the two diuretics were given concurrently and alternately with a drug-free day between doses. The edema cleared in one-half the time, 16 as against 32 days on the previous regimen. The formal assay (table 3) which included this patient (case 13) showed chlorothiazide to be less than one-half as effective as meralluride. With these facts, it was possible to understand why the daily weight losses during the use of chlorothiazide had ended at a time when meralluride was still effective. It involves a phenomenon illustrated in figure 3, which shows that when the patient had abundant edema, the chlorothiazide was almost as effective as the meralluride, but as the edema curve leveled off, the chlorothiazide days began to show no weight loss or a gain, while the meralluride continued to produce a loss with each dose. Our collective experience with these assays shows that, in the course of treatment, the closer the edematous patient comes to the edema-free state, the more resistant to a diuretic he becomes, and a weaker compound may even cease to cause any diuresis. This phenomenon is described more fully in the previous study.[2]

TABLE 3.—*Bioassay of Chlorothiazide in Bed-Patients in Congestive Heart Failure**

			Average Weight Loss per Dose, Lb.			Number of Paired Comparisons		
Case No.	Pattern	Total Edema, Lb.	Standard (S)	Test Drug (T)	Efficacy of Test Drug (T/S)	Standard Better	Test Drug Better	Standard Better (+) or Test Drug Better (—)
1	ABBA	7.0	1.25	0.5	40.0	2	0	+
2	BAAB	10.5	1.75	1.0	57.1	2	0	+
3	ABBA	7.5	1.25	0.5	40.0	2	0	+
4	BAAB	23.0	4.0	3.5	87.5	1	0	+
5	ABBA	7.5	1.5	0.5	33.3	2	0	+
6	BAAB	19.0	1.5	0.25	16.7	2	0	+
7	ABBA	7.0	2.25	1.25	55.6	2	0	+
8	BAAB	40.0	3.25	1.75	53.8	2	0	+
9	ABBA	30.0	1.25	0.25	20.0	1	1	0
10	BAAB	30.0	1.75	...	...	2	0	+
11	ABBA	12.0	2.0	0.25	12.5	2	0	+
12	BAAB	20.0	3.25	2.0	61.5	2	0	+
13	ABAB	45.0	4.75	2.44	51.4	3	1	+
14	BAAB	10.0	2.75	0.75	27.3	2	0	+
Average					39.7†			
Result						27	2	13(+),0(—)
Sign test result‡							19.9	11.08

* Standard, meralluride, 2 cc. I. M.; test drug, chlorothiazide, 2 Gm. orally.

† Confidence level at 5%: 26.3, 53.1.

‡ Sign test value exceeding 3.84 significant at 5%.

The assay values in patient 13 are of particular interest. The record for meralluride days showed an average weight loss of 4.75 lb. (2.14 kg.), chlorothiazide 2.44 lb. (1.11 kg.), and the days without a diuretic 2.09 lb. (0.95 kg.), hence only 12% more edema lost with chlorothiazide than without any drug. There have been many occasions to recall this negligible contribution to the "favorable impression" of the drug we gained during this patient's first hospitalization, in relation to similar impressions in reports of clinical trials carried out in the settling of a therapeutic regimen which fails to sort out the factors responsible for the attractive results.

With rare exceptions, it is the practice to make clinical comparisons of diuretics by administration of serial courses of the agents. The observations in this study show how deceptive this can prove to be. In patient 13 (figure 4) the daily weight loss for the first 10 days of the course of chlorothiazide averaged 2.35 lb. (1.07 kg.) per dose and for the similar course of meralluride which followed, only 1.1 lb. (0.5 kg.) per dose. By this method of testing, therefore, meralluride appeared to be only about one-half as effective as chlorothiazide. However, by the method of paired comparisons of concurrent doses in the same patient, the answer was reversed, meralluride appearing about twice as effective as chlorothiazide. The latter estimate received the support of the formal assay with 14 patients, which assigned to the 2-Gm. oral dose of chlorothiazide an efficacy value of about 40% of that of the 2-cc. intramuscular dose of meralluride. Attempts to restore balance in the method of serial courses by reversing the order of the drugs in one-half the patients are not altogether successful, since in this way another important variable is introduced, namely, different groups of patients for the comparisons.

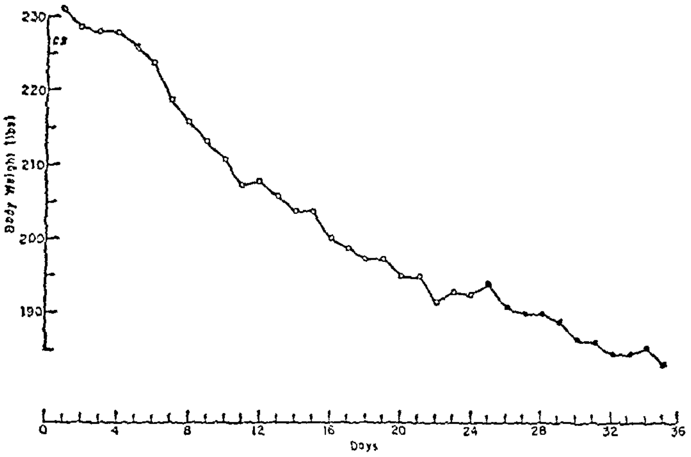

Fig. 4 (case 13 in tables 2 and 3).—Man, aged 68 years, with arteriosclerotic heart disease, enlarged heart, auricular fibrillation, obesity, and far-advanced congestive failure, treated with diet of milk and water, 1.5 liters of each, daily maintenance dose of 0.2 mg. of digitoxin, and daily dose of diuretic. Circles are 2-Gm. oral doses of chlorothiazide and dots 2-cc. intramuscular doses of meralluride.

Comment

Clinical opinion is generally agreed that oral administration of chlorothiazide is as effective as a parenterally given mercurial diuretic in patients with congestive failure. We examined the literature since the introduction of chlorothiazide a few years ago,[8] searching nearly 100 reports for data on valid comparisons with parenterally given mercurials. It would not be profitable to review the individual reports here, although it seemed worthwhile to list some of the characteristics of the various studies which left us with the conclusion that a reliable value for their relative efficacy in the matter of clearing edema had not yet been supplied.

The designs of the comparisons were usually unbalanced. In most of them the drugs were tested in serial courses, with the result that evaluations were made under conditions which were not comparable. The results with a diuretic depend as much on the plan of administration as on the efficacy of the drug, but chlorothiazide was often judged to be equal or superior to the mercurial from a comparison of the latter given twice a week with the former given daily. This fallacy was pointed out in a recent report.[9] In some of the studies chlorothiazide was declared comparable to the mercurial in spite of the fact that a large proportion of the patients still required supplementary doses of the mercurial. In some of the casual clinical trials, chlorothiazide was declared to be a major advance in diuretic therapy, the frame of reference being impressions of past experience with other agents. In several studies, the comparisons were made in terms not of the clearing of edema but of sodium excretion in patients who had recovered from congestive failure.[10] This involves (1) the difficulty that nonedematous patients are relatively insensitive to differences in the efficacy of diuretics as we have pointed out, and (2) the assumption that comparisons in terms of sodium excretion and edema loss give the same answers, which is not always the case.[11]

We thought it might be a matter of special interest to review in more detail the paper by Davies and Evans[12] who, while they also concluded that the 2-Gm. oral dose of chlorothiazide is as effective as the 2-cc. intramuscular dose of mersalyl or mercaptomerin and made the comparisons in serial unbalanced courses, used a method in some respects similar to ours and supplied data affording a means of examination for a possible explanation of the different answers. The essential points are summarized in table 4. The most significant difference in the methods was the fact that they compared the total 48-hour effect of two daily doses of 2 Gm. of chlorothiazide with the total

48-hour effect of only one 2-cc. dose of the mercurial, which calls for multiplying by two the value they assigned to the mercurial or dividing by two the effect of chlorothiazide.

We found in a previous study with a group of 20 patients in congestive failure (84 doses) that a 2-cc. intramuscular dose of meralluride on each of two successive days caused a similar 24-hour weight loss with each dose, namely, 3.6 lb. (1.63 kg.) for the first dose and 3.2 lb. (1.45 kg.) for the second. We also observed, in another group of 24 patients in congestive failure (123 doses), with the dose given only on the first day, that from the weight changes in the second (drug-free) day, the 48-hour period for the measured effect might prove misleading, especially if applied to small numbers of patients and doses, since for 19% of the 123 doses, the second day showed no change, for 34% an additional weight loss equal to 38% of that of the first day, and in the case of 47% of the doses, the gains on the second day erased nearly one-half (44%) of the weight losses of the first day. The result in this group was an average weight loss of 2.6 lb. (1.17 kg.) for the first 24 hours and a net gain of 0.1 lb. (0.05 kg.) in the second (drug-free) 24 hours, hence, an approximately 5% higher value for the 24-hour than for the 48-hour effect of the 2-cc. dose of the mercurial.

TABLE 4.—*Efficacy of 2 Gm. of Orally Given Chlorothiazide in Comparison with 2 Cc. of Intramuscularly Given Mercurial*[*]

	Original Data[†]		Revised Data[‡]	
	Mercurial	Chlorothiazide	Mercurial	Chlorothiazide
Patients, no.	17	20[‖]	14.0[¶]	14.0[¶]
Doses, no.				
Total	117	185	96.0	130.0
Average per patient	...	...	6.9	9.3
Standard error	...	...	±7.1	±3.8
Diuretic effect (oz. urine)				
Total per dose	416	945	442.0	517.0
Average per patient	+24	+47	+34.0[#]	+37.06
Ratio of averages C/M, %	...	196	...	109.0
Efficacy of chlorothiazide computed from C/M for each patient				
Average C/M, %[§]	...	...	...	69.6
Standard error	...	...	...	±38.9

[*] Based on data from Davies and Evans.[12]

[†] 48-hour response, chlorothiazide given on each day and mercurial only on first day.

[‡] Comparing 24-hour response to single dose of each drug.

[§] Confidence limits at 5%: 49.7 and 96.3

[‖] Includes 3 patients who did not receive mercurial.

[¶] After 3 patients excluded because of no diuresis with "standard" as required by new method.

[#] Includes 5% correction for weight gain in second 24-hour period.

It may be noted from table 4 that by revisions which made the two methods more nearly comparable, the original value, which indicated that the 2-Gm. oral dose of chlorothiazide was nearly twice as effective (196%) as the 2-cc. dose of the mercurial, fell off to 69.6%, an estimate close to the range in our assay. The sign test applied to the revised group supported the estimate in terms of ratios. Of the 14 patients, 12 "preferred" the mercurial and 2 the chlorothiazide, yielding 5.79, a significant value at the 5% level.

The results of the present study remain in sharp contrast to the prevailing opinion. This assay, showing that the 2-Gm. oral dose of chlorothiazide produces an average maximum diuretic response equivalent to about 40% of that of 2 cc. or 70% of that of 1 cc. of intramuscularly given meralluride, places the efficacy of chlorothiazide within the general range of other oral diuretics assayed by our earlier method in ambulant patients in congestive failure by the use of dose-response curves; namely, chlormerodrin (Neohydrin),[13] amisometradine (Rolicton),[11] and ethoxzolamide (Cardrase).[14] It would be a matter of interest to reassay these by the new method.

We should call attention to the fact that the evaluation of chlorothiazide in this study is not concerned primarily with whether orally given chlorothiazide is a useful diuretic but with a different point of fact, namely, how effective it is in comparison with parenterally given mercurial diuretics. It may be mentioned parenthetically that the diuretic response to agents with this order of efficacy may be considerable. It amounted to an average 24-hour weight loss of about 2 lb. (0.9 kg.) in a group of 73 ambulant patients in congestive failure.[4] The physician is to judge whether or not this diuretic potential is adequate in a particular case. The fact remains that it falls far short of the diuretic potential of the organic mercurial, for the 2-cc. dose of the mercurial given by intramuscular injection yielded an average 24-hour weight loss of nearly 4 lb. (1.8 kg.) in the same patients.[4]

It may be worthwhile to reemphasize a few points concerning the estimate of orally given chlorothiazide in relation to the parenterally given mercurial as revealed by this method of assay for therapy in the patient with congestive failure. It should be noted that the method does not involve any so-called "control" periods, nor any especially contrived experimental restrictions which sometimes render a result invalid for the case of the more casual setting in the practical care of patients. The data are supplied by unselected patients in congestive heart failure, at rest, maintained under the conventional conditions for the care of such patients (diet, salt restriction, and digitalization), in the course of a regimen of treatment that is highly effective and sanctioned by general experience. The results do not involve any assumptions about the mechanism of action. They provide a direct expression of relative efficacy of the agents in the matter of clearing edema. In these respects the assay method is like any ordinary treatment. The differences lie simply in the facts that the patient is weighed accurately every 24 hours under conditions that are constant with respect to obvious factors which may affect weight, that any therapeutic dietary regimen decided on is maintained fairly constant throughout the few days of the assay, and that the sequence of the doses of the two agents is so arranged as to provide paired responses free of bias. These are the factors that insure a reliable answer with relatively few patients and in a short time. Since the response time for any dose in the assay is the same for both agents, the ratios obtained express the difference in the time it will take to clear the edema if one of the drugs alone were used.

The present assay, in which chlorothiazide was assigned 40% of the efficacy of the mercurial, signifies that it could take two and one-half times as long to clear the edema with a 2-Gm. oral dose of chlorothiazide given daily or every other day as with a 2-cc. intramuscular dose of meralluride given in the same way. In a particular case of advanced failure taken as an example, if it would take 20 days to restore the patient to the edema-free state with the chlorothiazide, it may be expected that the mercurial would accomplish the same result in 8 days. From our experience the shorter period to secure the desired results is usually advantageous, although there are cases in which reactions call for a slower course. The decision remains a judgment of the physician.

Summary and Conclusions

Contrary to the prevailing clinical opinion, which holds that the 2-Gm. oral dose of chlorothiazide is as effective as the 2-cc. intramuscular dose of meralluride in patients with congestive failure, the present study shows that it is only about 40% as effective and that it takes an average of two and one-half times as long to clear the edema with chlorothiazide as with meralluride. This result, verified by standard statistical tests, was obtained by a new method for comparison of diuretics in patients in congestive heart failure, and there is reason to believe that it is directly applicable to the practical matter of clearing edema in therapeutic practice, since the assay is carried out within the framework of a conventional regimen of treatment which is highly effective and sanctioned by general experience.

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ACUTE HYPERTENSION DURING ANESTHESIA—THE UNSUSPECTED PHEOCHROMOCYTOMA

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The existence of a pheochromocytoma was found to explain hypertensive episodes which occurred during anesthesia in two patients. In one, a 25-year-old man, the first two episodes occurred during an attempt to excise an intracranial tumor. At a subsequent operation this tumor was completely removed, but attempts to remove the primary retroperitoneal tumor were unsuccessful because it had invaded surrounding structures. In the other patient, a 51-year-old man, a sudden rise of systolic blood pressure to 260 mm. Hg occurred during a lumbar sympathectomy. The suspicion of pheochromocytoma was verified when autopsy revealed a tumor in the left adrenal gland which weighed 1.4 kg. Sudden hypertension during surgical anesthesia should be treated with the urgency associated with cardiac arrest. In one case it responded promptly to administration of phentolamine. The possibility that a pheochromocytoma may be present should then be investigated.

The development of acute hypertension during anesthesia or an operation may be due to the presence of an unsuspected pheochromocytoma. An awareness of this concept is of practical importance, since the administration of an adrenolytic drug may be the only method available to control dangerous hypertension. This awareness will provoke investigative studies to confirm the presence of a pheochromocytoma, and it may lead, therefore, to a complete cure from a previously unsuspected fatal disease.

Two case histories are described in this report. Each patient had a pheochromocytoma, which was not suspected until severe hypertension developed during anesthesia.

Report of Cases

Case 1.—A 25-year-old man was admitted to Indiana University Medical Center on Oct. 26, 1956. He complained of progressive deterioration of vision in his left eye, occasional headaches, and transient numbness and tingling in his left arm since February, 1956. He knew that he had a heart murmur, which had followed an attack of rheumatic fever when he was a child, but he had no symptoms of cardiac disease.

Physical examination did not reveal any cardiac enlargement, but, on auscultation, a loud diffuse systolic murmur and an apical diastolic murmur were audible. His blood pressure was 150/90 mm.Hg and his pulse rate 90 per minute and regular. There was temporal pallor of his left optic disk and a central scotoma in his left visual field. Roentgenography disclosed demineralization of the left sphenoid ridge and around the superior orbital fissure. Cerebral angiography demonstrated a vascular tumor in the left anterior cranial fossa.

A left frontal craniotomy was performed on Nov. 11, 1956, and a tumor was discovered arising from the left sphenoid ridge. The tumor was partially excised. Anesthesia was induced by the intravenous injection of thiamylal (Surital) sodium. Succinylcholine chloride was administered intravenously to provide adequate relaxation, and an endotracheal tube was inserted with ease. A mixture of nitrous oxide and oxygen and intermittent intravenous injections of thiamylal and meperidine (Demerol) hydrochloride were used to maintain anesthesia.

The patient tolerated the operation well. His systolic blood pressure was elevated briefly to 200 mm.Hg on two occasions. When anesthesia was deepened, the blood pressure was restored to its normal level. It had been intended to provide controlled hypotension during the operation, but the intravenous injections of trimethaphan camphorsulfonate (Arfonad) and hexamethonium chloride (Bistrium), in adequate doses, did not depress the blood pressure. The patient recovered rapidly from this operation and was discharged from the hospital on Nov. 16. Histological examination of the tumor

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revealed an undifferentiated anaplastic neoplasm, but no more specific diagnosis was advanced.

In April, 1957, he developed congestive cardiac failure and was treated by his family physician. Treatment consisted of a salt-restricted diet, administration of digitoxin and cortisone, and bed rest at home. He responded well to this regimen.

On May 15, 1957, the patient was readmitted to this medical center. It was proposed to excise the remaining portion of the tumor. On this occasion, the patient's blood pressure was 160/80 mm.Hg and his pulse rate 90 per minute and regular. An electrocardiogram showed evidence of left-sided ventricular hypertrophy and digitalis effect. Digitoxin therapy was continued, and a course of preoperative cortisone therapy was commenced.

Secobarbital, 100 mg., and scopolamine, 0.4 mg., were administered intramuscularly at 6:30 a.m. on May 17. The patient's blood pressure was 160/70 mm.Hg and his pulse rate 100 per minute when he arrived in the operating room at 7:15 a.m. Anesthesia was induced and maintained as during the previous craniotomy. Immediately after the induction of anesthesia, his blood pressure increased to 200/130 mm.Hg, and his pulse rate rose to 110 per minute. The blood pressure remained at this high level during the next hour, and his pulse rate increased to 130 per minute. The level of anesthesia was deepened by the intravenous administration of thiamylal, secobarbital, meperidine, and promethazine (Phenergan) hydrochloride. The blood pressure gradually declined to 130/70 mm.Hg, but his pulse rate increased to 160 per minute. An electrocardiogram, which was obtained at this point, demonstrated a sinus tachycardia. Lanatoside C, 0.2 mg., was injected intravenously on two occasions; his pulse rate decreased to 120 per minute for about 20 minutes but thereafter increased to 140 per minute. His respiratory rate during the first two hours ranged from 20 to 30 per minute. The patient appeared cyanotic, despite an increase in the inspired oxygen concentration to 50% and later to 100%. A diagnosis of congestive cardiac failure was made, and the operation was abandoned. The blood pressure fell below 80/50 mm.Hg during the last hour of anesthesia and had to be maintained by repeated intravenous injections of methoxamine (Vasoxyl) hydrochloride.

The patient was taken to the recovery room, where his rectal temperature was found to be 105.2 F (40.7 C). His blood pressure had declined to 60/40 mm. Hg, and an intravenous infusion of norepinephrine bitartrate was administered to maintain the systolic blood pressure above 100 mm.Hg. His pulse rate was 120 per minute. Hydrocortisone sodium succinate (Solu-Cortef) and a further dose of lanatoside C were injected intravenously, oxygen was administered by nasal catheter, and his body was sponged with alcohol during his stay in the recovery room. His temperature gradually decreased, his color improved, and his blood pressure and pulse stabilized at the preoperative level.

The patient recovered so well during the next two weeks that it was suggested that the operation should be attempted again on June 8. His physical condition had been restored to its previous state, and the only new complication was a mild degree of trismus, which was the result of the healing craniotomy incision. The trismus did not appear to be sufficient to prevent direct laryngoscopy. Digitoxin and cortisone were administered to prepare him for surgery.

Secobarbital, 150 mg. and scopolamine, 0.4 mg. were injected intramuscularly as preanesthetic medication, and when the patient arrived in the operating room one hour later he was awake but calm. Thiamylal and succinylcholine were injected intravenously, and an endotracheal tube was inserted with some difficulty because of the trismus. A mixture of nitrous oxide and oxygen was administered to maintain anesthesia. Immediately after the induction of anesthesia, his blood pressure was 210/100 mm.Hg and his pulse rate 120 per minute. The hypertension persisted, but the pulse rate declined to 80 per minute. The patient coughed violently as his scalp was cleansed, and his blood pressure increased to 260/100 mm.Hg and his pulse rate to 130 per minute. Further injections of thiamylal and succinylcholine were made to deepen the level of anesthesia and to control the cough. A fresh soda-lime canister was inserted into the machine; the patient was hyperventilated, but his hypertension persisted. Trimethaphan, 250 mg., was administered rapidly by intravenous infusion. This had no effect on his blood pressure, but the pulse rate increased to 170 per minute.

The situation was reevaluated. The patient had a cold, pale, dry skin and marked cutis anserina, despite a rectal temperature of 102.4 F (39.1 C). His pupils were widely dilated, and he was now cyanotic despite the administration of 100% oxygen by intermittent positive pressure. The possibility that this crisis was due to the presence of an unsuspected pheochromocytoma was considered. Phentolamine (Regitine) hydrochloride, 5 mg., was injected intravenously and, although the tachycardia persisted, his blood pressure decreased rapidly to 140/90 mm.Hg.

It was decided to defer the operation until diagnostic tests had been carried out to confirm the tentative diagnosis of pheochromocytoma. The patient was awake when he arrived in the recovery room. His temperature fell to 99.2 F (39.2 C) during the next hour, and his pulse rate decreased to 100 per minute. The cyanosis disappeared, and his blood pressure remained at the preoperative level.

The severe hypertension did not recur during the postoperative period, and the patient again recovered rapidly from the critical episode. The phentolamine (Regitine) and histamine tests were carried out, but the results were inconclusive. Urinary catechol amine levels were markedly elevated. Roentgenographic examinations were repeated and disclosed the presence of a rounded mass in the region of the left adrenal gland and a spherical nodule in the lower lobe of the left lung. The histological specimens of the brain tumor were reexamined, and a diagnosis of paraganglioma was suggested. It was agreed that this could be a metastatic lesion, secondary to an adrenal pheochromocytoma.

A craniotomy was performed successfully on June 28. Local infiltration of the scalp with 0.5% lidocaine hydrochloride, without epinephrine, was used to provide anesthesia. The tumor was found to have diminished in size, and the small portion which remained was completely excised. During the injection of the local anesthetic solution the patient's blood pressure increased to 250/120 mm.Hg but returned rapidly and spontaneously to the preoperative level and remained there throughout the remainder of the operation. He was discharged from the hospital on July 5.

The patient was readmitted to the medical center on Sept. 14, 1957. The clinical diagnosis of malignant pheochromocytoma appeared to have been established. It was decided that the primary tumor and the pulmonary metastasis should be excised, for it was hoped that this might retard the progress of the disease, or might even cause a regression. The primary tumor was exposed during operation and was found to have invaded the surrounding structures. The abdominal aorta and the celiac axis were damaged during the excision of the tumor. An attempt was made to repair these large vessels, but the patient died shortly after his return to the recovery room. Pathological examination of the tumor confirmed the preoperative diagnosis of malignant pheochromocytoma.

Case 2.—A 51-year-old man was admitted to Indiana University Medical Center on Nov. 7, 1958. His feet were edematous and discolored, and there was infected gangrene of the fourth and fifth toes of his left foot and of the fourth toe of his right foot. The femoral pulses were the only ones palpable in either leg. His blood pressure was 140/80 mm.Hg and his pulse was regular at a rate of 90 per minute. There was no cardiac enlargement, but a loud systolic murmur was audible in the aortic area. An electrocardiogram revealed the presence of multiple auricular extrasystoles but showed otherwise normal findings.

It was decided that a bilateral femoral arteriogram should be obtained under general anesthesia on Nov. 10. His blood pressure was 150/70 mm.Hg and his pulse rate 72 per minute when he arrived in the radiology department. Anesthesia was introduced with methohexital (Brevital) and maintained with a mixture of nitrous oxide and oxygen. A bilateral femoral arteriogram was obtained, and it was proposed that a bilateral lumbar sympathectomy be carried out. The patient's blood pressure and pulse had remained at normal levels during the procedure. He was allowed to awaken from the anesthetic and was taken to the operating room.

Anesthesia was induced again with methohexital and was continued with cyclopropane. A solution of 0.2% succinylcholine was infused intravenously to provide muscular relaxation. A transabdominal extraperitoneal approach to the sympathetic chain was used.[1] The blood pressure and pulse remained stable at the preoperative level during the excision of the right lumbar sympathetic chain. As the surgeon exposed the left sympathetic chain, the blood pressure increased to 260/170 mm.Hg, although the pulse rate remained at 80 per minute. When the left lumbar sympathetic chain had been excised, the blood pressure declined spontaneously to 140/80 mm.Hg and the pulse rate remained between 60 and 80 per minute. It was suggested to the surgeon that this patient might have a pheochromocytoma of his left adrenal gland, and he agreed to investigate this possibility during the postoperative period.

The urinary catechol amine levels were estimated and were markedly elevated. It was not possible to perform any of the other diagnostic tests, since the patient developed right-sided hemiplegia and aphasia on the second postoperative day. The blood pressure was measured every two hours after his return to the ward, and the highest value recorded was 180/90 mm.Hg. The patient developed auricular fibrillation, and his temperature fluctuated between 101 to 104 F (38.3 to 40.0 C). Despite the administration of phentolamine by continuous infusion, digoxin, and tetracycline (Achromycin), the patient's condition deteriorated and he died on Nov. 20, 1958.

Postmortem examination revealed the presence of a pheochromocytoma of the left adrenal gland, which weighed 1,435 Gm. (50.6 oz.) (normal is 7 Gm. [0.2 oz.]). The superior mesenteric artery was thrombosed, there was necrosis of the distal half of the ileum, and there was a massive infarct of the right kidney. Examination of the brain was not permitted.

Comment

A pheochromocytoma is a rare tumor which occurs in the adrenal medulla, or wherever chromaffin tissue is found. These tumors, which are of importance in hypertension, are found as a rule in, or adjacent to, the adrenal gland. Less than 10% of these tumors are malignant.[2] The pathophysiological effects that are associated with the pheochromocytoma are due to an excessive secretion of norepinephrine by the tumor.[3]

Smithwick and co-authors [4] reported that in their series of patients, who were to be treated by extensive sympathectomy for hypertension, 0.5% had pheochromocytomas. Graham [2] estimated that pheochromocytomas are responsible for the death of 800 persons in the United States every year. Some of these persons undergo surgery for another reason, and their response to anesthesia and surgery may prove fatal. Apgar and Papper [5] pointed out that the danger of performing unrelated surgical procedures on patients with pheochromocytomas is associated with a mortality of about 50%. If the significance of the dangerous response is recognized, it may lead to the recognition of an unsuspected disease and to a complete cure from this fatal disease. Unfortunately, of all cases of pheochromocytoma, 70% are diagnosed only post mortem.[6]

Death usually occurs as the result of the hypertensive crisis.[6] The hypertension may lead to cerebral hemorrhage, pulmonary edema, ventricular fibrillation, or acute ventricular failure. Severe and fatal secondary hypotension may follow the hypertension. This hypotension may be due either to the cessation of the excessive secretion of catechol amines by the tumor, to its continuation,[7] or to continuing left ventricular insufficiency. Occasionally a chronic adrenal insufficiency may be superimposed.[8] These causes do not explain the death of the second patient described in this report. He developed acute arterial insufficiency, which involved the brain, the kidney, and the ileum and which was responsible for his death. The combination of an active pheochromocytoma and peripheral atreriosclerosis appears to offer a reasonable explanation for the postmortem findings.

The first patient survived two anesthetic and surgical procedures before the presence of a pheochromocytoma was suspected. This was not surprising, for his response to the first operation was not particularly abnormal, and during the second operation the presence of known rheumatic heart disease appeared to be sufficient to explain the crisis. Hypertension was the dominant abnormality during the third procedure, and it was because of this feature that the presence of a pheochromocytoma was considered. The patient's rapid response to administration of phentolamine strengthened this suspicion and, more important, allowed control of a dangerous situation. The hypoxia and hypercarbia, which probably developed during the difficult endotracheal intubation in an apneic patient and during the violent coughing, were the factors responsible for initiating the crisis. The transient hypertension which occurred during the fourth craniotomy, while the local anesthetic solution was being injected, was probably due to an associated emotional disturbance. The second patient exhibited severe hypertension when the adrenal gland was retracted to expose the sympathetic chain. Phentolamine was not used on this occasion, since the hypertension subsided rapidly.

Bartels and Catell [9] emphasized that these hypertensive cases constitute an extremely dangerous situation and that they should be treated with all the urgency associated with a "cardiac arrest." They suggested that one of the following courses be instituted: (1) immediate discontinuance of the operation and subjection of the patient to further investigative study after recovery; (2) in intra-abdominal operation, immediate exploration of the adrenals and the sympathetic chain areas and, should a tumor be found, execution of steps to proceed with its removal; or (3) use of an adrenolytic drug to control hypertension, followed by continuance of the initial operation, and execution of postoperative investigation to confirm the presence of a pheochromocytoma (the response of the blood pressure to the adrenolytic drug providing additional confirmatory evidence).

The only point of contention which might arise is whether it is advisable to resect a pheochromocytoma if it is discovered during the course of an intra-abdominal operation. It is important to stress that an operation to remove a pheochromocytoma is a hazardous procedure requiring skill and experience in both surgeon and anesthesiologist. It is better that the operation be deferred if this skill is lacking in either member of the surgical team, or is not readily available.

Summary

Two cases, described in this report, illustrate that the development of acute hypertension during anesthesia and surgery may be due to the presence of an unsuspected pheochromocytoma. The first patient had a malignant pheochromocytoma, which appeared to be an intracranial tumor. Hypertension developed during anesthesia for his third craniotomy. The hypertension responded readily to the administration of phentolamine (Regitine) hydrochloride.

The second patient developed hypertension during a lumbar sympathectomy. His death, during the postoperative period, was due to acute arterial insufficiency, which involved the brain, kidney, and ileum. It is suggested that this was due to the combination of an active pheochromocytoma and peripheral arteriosclerosis. In both cases the clinical diagnosis of pheochromocytoma was established post mortem.

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A TUMOR-PRODUCING VIRUS.—Stewart and her colleagues isolated a filterable agent and found it to produce a wide variety of tumours when inoculated parenterally into very young mice, hamsters, and rats. This "polyoma" virus was present in extracts of induced mouse parotid-gland tumours and in spontaneous leukaemias, and multiplied in cultures of monkey kidney or mouse-embryo cells. The virus was cytopathogenic for the cultures, resisted heating to 56° C., was insensitive to ether, and haemagglutinating for guinea-pig, rat, and human Group O cells at +4° C., but not at room temperature. . . . A virus, which we have called "M. H. polyoma," with properties similar to Stewart and Eddy's "polyoma" virus has been isolated in tissue culture from the spleen of a leukaemic AK mouse. When inoculated into suckling mice, rats, and hamsters, the virus produced a variety of tumours and other lesions. Some of these tumours—renal sarcomata in hamsters and a mouse mammary carcinoma—were serially transplantable. In the hamster tumours the presence of the virus was only revealed by infecting tissue cultures of mouse-embryo fibroblasts. Electron-microscopy of infected tissue cultures showed many particles 30-40 mμ in diameter in the cell nuclei, and fewer, larger particles, with external membranes, in the cytoplasm.—G. Negroni, M.D., R. Dourmashkin, M.D., and F. C. Chesterman, M.B., B.S., M.I. Biol., A "Polyoma" Virus Derived From a Mouse Leukaemia, *British Medical Journal*, Dec. 19, 1959, pp. 1359-1360.

MARROW EMBOLISM AND INTRAOSSEOUS CONTRAST RADIOGRAPHY

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A contrast medium was injected into the medullary cavity of the right femur in order to visualize the vascular pattern of the marrow for diagnostic purposes, the patient being a 60-year-old woman with widely metastasizing carcinoma. At death, emboli consisting of marrow cells and a bone spicule were found in the pulmonary vessels. This is believed to be the first proved case of marrow embolism after intraosseous contrast radiography, but evidence from various sources indicates that injections into the bone marrow entail certain hazards.

There are many current reports dealing with intraosseous venography and visualization of the vascular pattern of the marrow.[1] Nearly all stress the relatively innocuous nature of this study. We performed five of these examinations, hoping to find patterns of vasculature which would be characteristic of tumors and the leukemia-lymphoma group of diseases. In one of our patients who died and on whom an autopsy was performed the day after the study, we found well-preserved marrow cells and a spicule of bone in pulmonary arteries. We believed that the case should be reported to point out a possible hazard which has not yet been encountered by others who have carried out intraosseous contrast radiographic examinations.

Report of a Case

The patient was a 60-year-old woman, who was admitted to the Medical Center on July 31, 1957, with a history of weight loss and constipation for three months, followed by passage of blood per rectum. An annular carcinoma of the rectum was found, and subsequently an abdominoperineal resection of the rectum was performed. Metastases were present in regional lymph nodes and the liver contained two nodules which, on gross examination, were suggestive of tumor at operation. The patient did well for three months after operation and then began to complain of right upper quadrant pain. At the time of her last admission in December, 1957, she had pain in the right hip. She then became aphasic and was unable to walk. A follow-up roentgenogram of her chest now revealed pulmonary metastases. The patient became semistuporous. On Jan. 3, 1958, intraosseous contrast studies were made. A solution of 20 cc. of 50% diatrizoate (Hypaque) sodium was injected manually through a marrow needle inserted into the right femur, in an attempt to demonstrate metastatic involvement of the marrow cavity (fig 1*a* and *b*). The patient died the next day.

The microscopic examination of the lungs showed areas of hemorrhage and necrosis. Other areas were atelectatic and infiltrated by polymorphonuclear leukocytes. Tumor infiltration was also seen. The hemorrhagic areas were generally wedge-shaped and were located beneath the pleura. The pulmonary veins were distended with blood. Some contained tumor thrombi. Many pulmonary arteries contained thrombi, some of which consisted of tumor cells. In larger vessels thrombi were seen, consisting of fibrin masses, each covered by endothelium, resembling fibrinous endocardial vegetations. The walls of the adjacent vessels were occasionally infiltrated by polymorphonuclear leukocytes, as were the occasional thrombi. Other thrombi appeared fibrillar and laminated. Proximal to one such thrombus, in a 2-mm. artery, there was a fragment of marrow filling the vessel distally and interdigitated with the thrombus. (fig. 2 and 3.) It was generally well-preserved and included one spicule of calcified material, about 40μ in the greatest diameter. Marrow emboli were seen in several other arteries, the largest being 5 mm. in diameter.

Other pertinent autopsy findings included (1) colostomy and scar in the left lower abdominal quadrant, with surgical absence of the anus, the rectum, and an ovary (surgical pathologist's report: infiltrating adenocarcinoma of the rectum, with metastases to regional lymph nodes, and simple ovarian cyst); (2) metastatic mucin-producing adenocarcinoma to lymph nodes of the periaortic and portal areas, liver, and lungs; (3) nonbacterial thrombotic endocardiosis with vegetations of the mitral and aortic valves, thrombi of the left posterior communicating cerebral artery, with infarcts of the left basal ganglions and cerebral peduncle, and thrombi of the pulmonary arteries and hepatic veins and of the arterioles of the heart, kidneys, and spleen, producing renal and splenic infarcts; (4) arteriosclerosis of the aorta and the cerebral vessels; and (5) bilateral hydronephrosis and chronic pyelonephritis. Of interest was the finding of endocardial vegetations resembling fibrin associated with multiple similar fibrin thrombi in other organs. This phenomenon has been seen in other instances of mucin-producing carcinomas.[2]

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Comment

Intraosseous contrast studies were first described in 1940 by Benda, Orinstein, and Depitre [1b] and by Henning.[1a] Injections have been made into the spinous processes [1h] for evaluation of the azygous and thoracoabdominal veins. The femoral trochanters [11] and the pubic bones [1e] have been injected to visualize pelvic veins. The calcaneus has been reported as an excellent site for deep vein visualization of the lower extremity, but some have reported a preference for the medial malleolus of the tibia,[11] while the head of the fibula has been preferred by others.[1m] Injections into the distal radius have been performed [1f] to evaluate the upper extremity. Attention was focused on the pattern of vessels in the medullary cavity by Menegaux and co-workers.[1k] Normal patterns, as well as those seen in cases of fractures, osteomyelitis, bone malignancy, and other conditions have been studied.

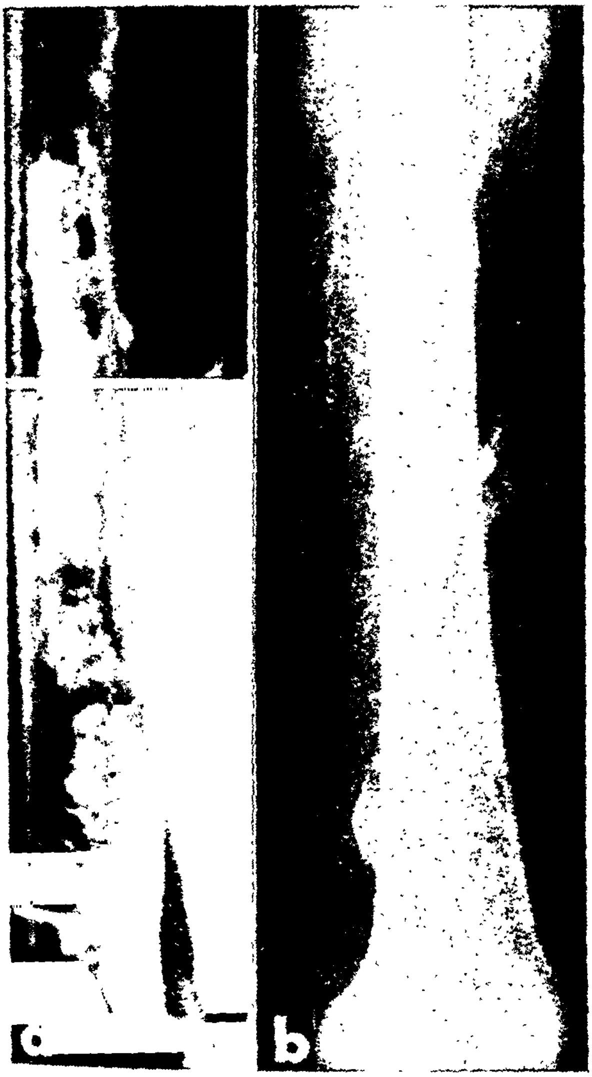

Fig. 1.—*a*, Fluoroscopic spot films of vascular pattern of femoral marrow and associated deep venogram. *b*, Film made after completion of intraosseous injection of 50% diatrizoate into femur.

In all of these reports there have been no instances in which marrow emboli were noted. The most frequently observed complication is the pain associated with the injection. Lester and Lampe [11] recently reviewed the literature pertaining to complications associated with intraosseous venography. They found that most authors [3] dismiss the subject, having observed few or no ill-effects. References were made to local reactions when the contrast agent extravasated about the injection site. Febrile responses were occasionally seen. One patient developed clinical signs of a pulmonary infarct immediately after pelvic venography.[1e] The question whether the embolus was due to a thrombus dislodged from pelvic veins or to marrow fat was not answered, since the patient recovered.

There have been a few cases of bleeding after pelvic venography.[1e] Several reports [4] contained comment on injury of the bone and local marrow space, which healed with no major sequelae. Lester and Lampe [11] observed the following complications in some of their 14 cases: local reactions, pain, fever, delayed hemorrhage, and thrombophlebitis.

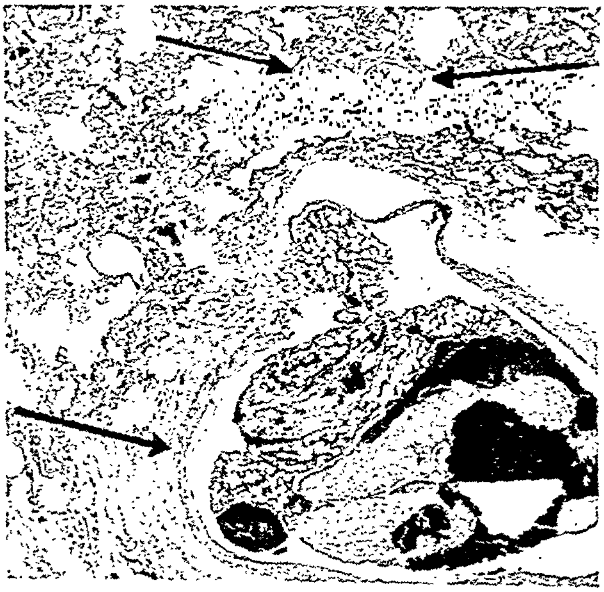

Fig. 2.—Multiple marrow emboli in pulmonary arteries (low-power magnification).

In our five cases, all patients experienced pain in varying degrees during the intraosseous injection of the contrast agent. We encountered the marrow emboli in our fifth case. After we had had this experience, a report appeared in the literature describing a case of marrow embolism after a sternal puncture.[5] There was also a brief report [6] of one patient who developed a fatal embolus after a sternal puncture.

In fat embolism studies performed on dogs, Bloomenthal, Olson, and Necheles [7] were able to produce fatal pulmonary emboli by injecting a water-soluble agent, iodopyracet (Diodrast), under pressure, through a femoral marrow cannula. When water-soluble agents were infused slowly into the marrow cavity of the tibia or femur of dogs, Macht[8] found the route to be as safe as the intravenous route. Tocantins and O'Neill[9] agreed with this thesis, and they used the marrow route for 52 infusions in 40 patients, with no ill-effects. They concluded that "although some fat is conceivably displaced into the blood stream, there is little ground for fearing any such complication as 'fat embolism.'" They calculated that it would require about 63 cc. of fat for a fatal embolus, and since the marrow site selected for infusion is a vascular site with low fat content, they believed there is little risk of fatality. This is probably true if the infusion is administered with ordinary pressures. However, if attempts are made to increase the speed of administration of the infusion by increasing pressures, the risk of fatal embolism would become great, as demonstrated in the animal experiments of Bloomenthal, Olson and Necheles.[7] Several of the reports [10] on intraosseous venography specify the use of pressure injectors to obtain uniform speeds of injection of the contrast mediums. The authors of one of these papers [11] also stated that the procedure requires 52 to 54 cc. of 50% diatrizoate for venography. The rapid injection of this volume of fluid could conceivably displace a significant volume of marrow fat in some patients, since Tocantins and O'Neill estimated that 63 cc. of fat would produce a fatal embolus. Although this has not yet been reported as a complication of marrow injections, we feel there may be definite hazard to the procedure.

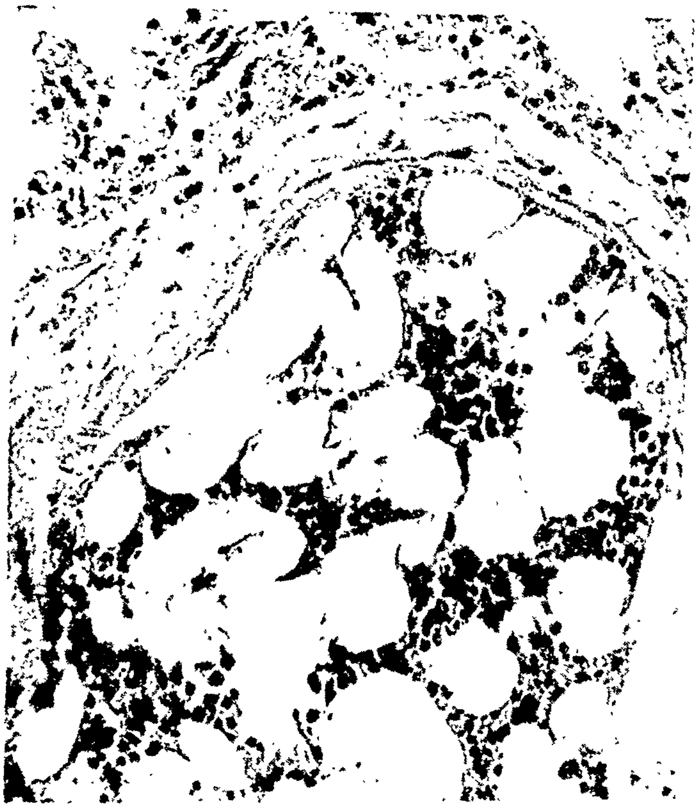

Fig. 3.—Marrow cells and fat in pulmonary artery (high-power magnification).

It also seems hazardous to inject into the marrow cavity in the presence of primary bone malignancies or metastatic deposits. We believe there is a danger of disseminating malignant cells in the same fashion that marrow was embolized in our patient as well as in the other cases,[11] in which only sternal puncture was performed.

Summary

Marrow cells and a bone spicule were embolized to pulmonary vessels in a patient in the course of intraosseous contrast studies. We believe this is the first proved instance of this complication. Some experimental and clinical studies of injection of infusions and contrast agents into the marrow cavities, as well as the present report, emphasize the potential hazards of this procedure, particularly when fluids are injected with increased pressures produced by mechanical devices.

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PERCUSSION OF THE STERNUM

I. AID TO DIFFERENTIATION OF PERICARDIAL EFFUSION AND CARDIAC DILATATION

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The relative advantages of percussion and of single roentgenograms were studied in 32 cases of pericardial effusion. The diagnosis was established by actual demonstration of the presence of effusion fluid by paracentesis, biopsy, autopsy, or serial roentgenograms. The single roentgenogram gave the correct diagnosis in only 13% (4 of 32 cases), but percussion gave the correct diagnosis in 58% (17 of the 29 cases in which adequate records were available). The most reliable sign was a flat percussion sound over the lower half of the sternum; flat percussion sounds in the left third intercostal space adjacent to the sternum and on the right extending from the sternum between the third and sixth ribs were also often observed in this condition. The procedure of percussion can be simplified by fixing attention on areas of flat percussion sounds and disregarding intermediate degrees of dulness.

Percussion of the heart is a neglected, almost forgotten art. In the preroentgenographic era, percussion was an important diagnostic tool which was used with much skill and considerable success. The advent of the roentgenographic method seemed to render percussion of the heart superfluous. In 1936, Sir John Parkinson[1] warned: "No longer shall we tell of the professor who by knocking at the front door could find out who was in the drawing room." In many medical schools, at present, percussion of the heart is being taught half-heartedly, with a hint as to its negligible diagnostic value compared with the information yielded by the roentgenographic method.

Indeed, the advantages of the use of roentgenograms in the diagnosis of enlargement of the heart and its individual chambers are obvious and need not to be pointed out. Does this apply also to the recognition of pericardial effusion? To answer this question, 32 cases were studied in which the presence of pericardial effusion was ascertained by either paracentesis, biopsy, postmortem study, or observation of rapid changes in the size and shape of the heart silhouette as shown by serial roentgenographic studies. The diagnostic results obtained by a single roentgenographic examination and by percussion, respectively, were compared. One of several illustrative cases is reported below.

Report of a Case

A 57-year-old woman was admitted to the Maimonides Hospital on Jan. 17, 1953, for an operation for mitral stenosis. On physical examination, the lungs were clear and the apex beat of the heart was not palpable. A slight heaving pulsation was felt during systole in the left parasternal line between the fourth and sixth ribs. In that area, a loud first sound and an early diastolic rumble were heard. The second pulmonic sound was accentuated. A flat percussion note was elicited over the sternum from the level of the third costal cartilage downward (fig. 1). A similar percussion note was observed to the left of the sternum in an area about 2 in. wide in the third intercostal space, and in a smaller area in the second interspace. A flat percussion sound was also observed in the fifth intercostal space to the right of the sternum for a distance of about 3 in. The venous pressure was 144 mm. of water, rising to 164 mm. when pressure was applied to the abdomen. The circulation time (arm-to-tongue) was 27 seconds. A chest x-ray taken on Jan. 20, 1953 (fig. 2, *left*), was interpreted as being indicative of enlargement of the heart involving both ventricles. The left atrium appeared to be dilated to a moderate degree on "barium swallow."

The clinical diagnosis was mitral stenosis. The area of percussion flatness was far too extensive to be explained by mitral stenosis in the absence of evidence of a huge left atrium. Therefore, pericardial effusion was diagnosed, and the patient was referred to the roentgenologist for angiocardiography. The roentgenologist reported that fluoroscopy revealed "definite pulsations of all cardiac contours, as well as a positive response to the Valsalva procedure." Hence, angiocardiography was thought to be unnecessary, [illegible] roentgenographic diagnosis of cardiac enlargement was upheld.

Operation on the mitral valve was performed on Feb. 18, 1953. The pericardial sac contained about 500 ml. of fluid. A roentgenographic study which was made after the operation (fig. 2, *right*) showed shrinking of the heart silhouette and left-sided pleural effusion.

Comment

It is indisputable that roentgenographic examination is the supreme diagnostic tool for the determination of the size and shape of the heart and its individual chambers. However, the roentgenogram

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reveals but a shadow and yields no information about whether this is composed of muscle, blood, or serous fluid. The difficulties in distinguishing between a failing dilated heart and pericardial effusion by roentgenographic study are well known.[2] They were summarized in an editorial in *The Lancet*[3] as follows: "There is no simple radiographic method of diagnosis. . . . None of the many signs suggested in this connection is more than partly successful; some are based on a misconception of x-ray physics, while others ignore the principles of hydraulics."

The difficulties in the roentgenographic method of differentiating cardiac dilatation from pericardial effusion have been demonstrated by the results of the present study. In only 4 of 32 cases was a correct diagnosis of pericardial effusion made on the basis of a single roentgenographic examination. In all other instances, enlargement of the heart was the initial diagnosis. Pericardial effusion was not recognized until serial roentgenographic studies showed shrinking of the heart silhouette or until paracentesis revealed the presence of fluid in the pericardial cavity. This shows, as was stressed by the editorial in *The Lancet*,[3] that isolated roentgenographic studies are of little value. It is the changes observed in serial examinations that are diagnostically significant. That is to say, pericardial effusion is generally diagnosed when a striking reduction in the size of the heart silhouette is noted. At that stage, however, the diagnosis is of little practical value. The presence of fluid in the pericardium ought to be diagnosed when the condition is at its peak and when recognition may, at times, lead to life-saving therapy.

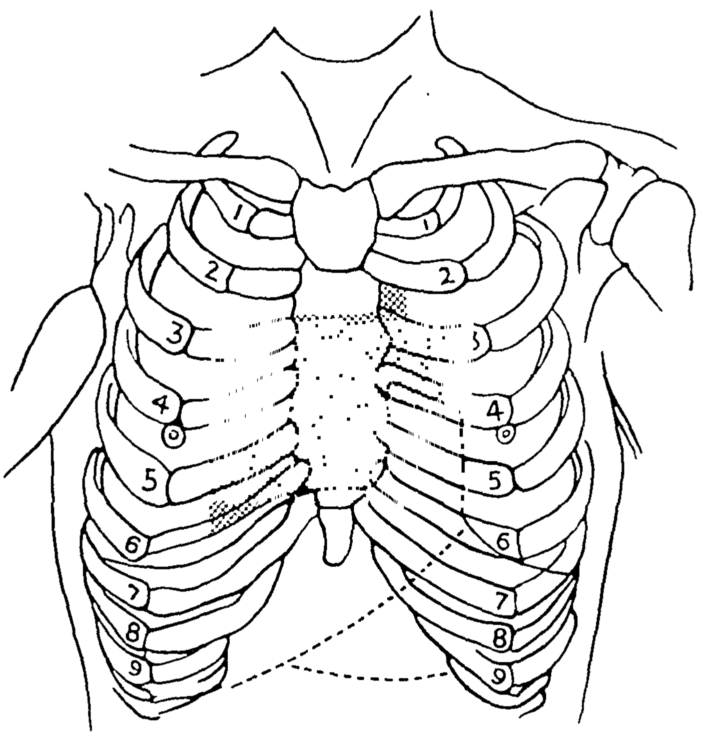

Fig. 1.—Percussion of sternum in differential diagnosis of pericardial effusion from cardiac dilatation: flat percussion sound (indicated by *cross-hatching*) was obtained over two-thirds of sternum and in adjacent areas to right and left of sternum.

The case records of the Massachusetts General Hospital[4] contain the report of a hypertensive patient who suffered from pneumonia with pneumococcic bacteremia. Postmortem study revealed the unexpected presence of 900 ml. of pus in the pericardial cavity. In discussing the case, the internist remarked: "The most distressing aspect of the case was the fact that the patient died without our having spotted what he actually had. If the diagnosis had been made, it is possible that with proper treatment he would have survived." The roentgenologist stated, "for the record," that the diagnosis could not be made from the films which failed to show "the typical cardiac configuration produced by pericardial fluid." The case history included no mention of percussion findings.

The shortcomings of the roentgenographic method have led to the use of auxiliary procedures, such as injection of carbon dioxide into the veins prior to roentgenographic study,[5] angiocardiography,[6] and cardiac catheterization.[7] These methods, while helpful, involve considerable strain and occasional risk for the patient; moreover, they may not be feasible in severely ill and debilitated patients. Percussion of the heart has no such drawbacks; what are its achievements?

In the present series of 32 cases, adequate records on percussion findings were available for 29 patients. Positive percussion findings were obtained in 23; in 17 (58%), they were characteristic enough in themselves to form the basis for a diagnosis of pericardial effusion.

Thus, in more than one-half of the cases, percussion proved to be a reliable method for the diagnosis of pericardial effusion. Other authors who have given the method a thorough trial reported similar experiences. Moschkovitz[8] stated that of all the signs conventionally used for the recognition of pericardial effusion, percussion findings were the most dependable. Why, then, was percussion of the heart virtually abandoned in some teaching institutions? This is only partly explained by the machine age's preference for laboratory evidence. The chief reason is the understandable trend toward eliminating the subjective factor in diagnostic methods. Indeed, attempts at percussing the borders of the heart by utilizing minor variations in the percussion sound ("relative dulness") open the door to gross errors. It has been shown that there is a tendency to underestimate the size of the heart on the right side and to overestimate it on the left side.[9] In percussing the right outline, the error may be greater than 4 cm.[10]

At the Maimonides Hospital we have abandoned percussing the outlines of the heart, and have dropped, as others did,[10] the distinction between absolute and relative dulness. Only marked degrees of dulness, approaching flatness, are utilized for diagnostic purposes. Agreement is readily obtained on what may be considered marked dulness or flatness. This is especially true in the case of pericardial effusion which, as a rule, yields a strikingly flat percussion sound. Instead of percussing the borders of the heart, we have chosen to evaluate the presence of abnormal areas of marked dulness. This simplifies the use of percussion and reduces the subjective factor of error.

The finding of an extensive area of flat percussion sound over the sternum has proved, in my colleagues' and my experience, to be the leading diagnostic sign in the presence of pericardial effusion. At this point it should be remembered that, in healthy adults with the heart in normal position, an area of dulness is found below the fourth rib, extending from the left sternal margin for a distance of from 1.5 to 2 in. to the left; that is, well within the left midclavicular line. The sternum itself, which covers the great vessels above the level of the third rib, the appendage of the right atrium, and part of the right ventricle below, normally yields a resonant percussion sound. This is usually fuller over the upper third of the sternum where the pulmonary layer covering the vessels is thicker than in the portion of the sternum below, which overlies the right ventricle.

Accumulation of fluid in the pericardial sac causes atelectasis and retraction of the mediastinal portions of the lungs, either by filling the retrosternal space or by forcing the heart forward through pressure from behind. Since a thick layer of lung tissue covers the great vessels, collection of fluid in the upper pericardial recessus is not as readily revealed by percussion as is fluid which accumulates in front of the right chambers of the heart. Only in one case of the present series was percussion dulness first noted over the manubrium sterni and the adjacent interspaces.[11] In most cases, pericardial effusion is indicated primarily by a flat percussion note elicited over the lower half of the sternum. The larger the effusion, the more likely is the flat percussion sound to creep higher up the sternum—indeed, sometimes as high as the level of the second costal cartilage (fig. 1).

While a massive sternal dulness is usually the first sign drawing attention to the presence of pericardial effusion, other areas of flat percussion sound are observed which yield confirmatory diagnostic evidence. One area is in the third left interspace, extending from the left sternal margin for a distance of from 2 to 4 in. to the left, even beyond the left midclavicular line. Occasionally, it encroaches on the second intercostal space. Another broad area of flatness is observed to the right of the sternum in the fifth intercostal space. Its diagnostic significance increases when it reaches upward into the fourth and third intercostal spaces.

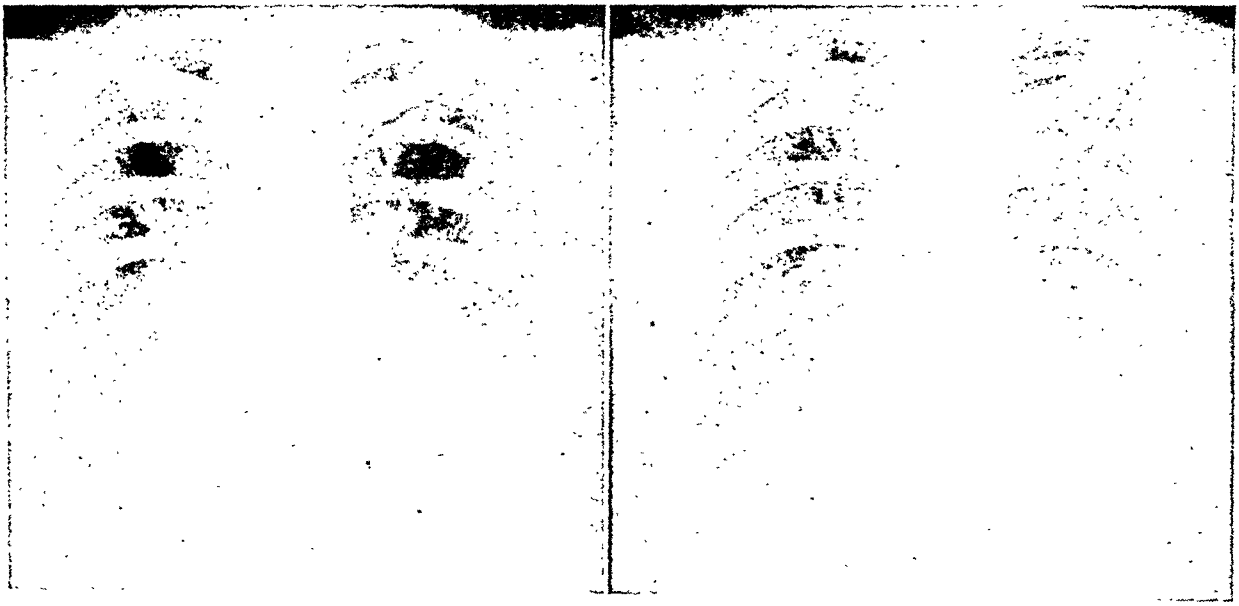

Fig. 2.—Roentgenograms of chest. *Left,* heart silhouette is bilaterally enlarged. *Right,* after mitral commissurotomy, size of heart silhouette is markedly reduced, and there is evidence of left pleural effusion.

Using these signs of percussion, my colleagues and I were able to diagnose pericardial effusion when it was at its peak and to advise surgical treatment when cardiac tamponade threatened. The method is simple enough to be taught to students. Indeed, in some instances of the present series in which cardiac enlargement was diagnosed on the basis of roentgenographic findings, the young members of the house staff became suspicious of pericardial effusion because of the percussion findings and suggested further study.

Changes in the percussion sound caused by pericardial effusion are, as a rule, easily distinguished from the signs of cardiac dilatation. As Auenbrugger pointed out from 100 years ago, pericardial effusion yields an unusually flat percussion note associated with a feeling of marked resistance, similar to that experienced on percussion of a "fleshy limb." Enlargement of the left ventricle causes no dulness in those areas in which a flat percussion note is characteristically produced by pericardial effusion. A dilated right ventricle, on the other hand, causes dulness at the lowest portion of the sternum; this, however, rarely extends beyond the level of the fifth costal cartilage (fig. 3). Dilatation of the right atrium due to heart failure causes dulness in a small area adjacent to the sternum in the right fifth intercostal space (fig. 3). This area of dulness does not extend to the right of the sternum for more than 1 in., nor does it reach upward beyond the fifth rib.

Marked dilatation of the pulmonary artery or outflow tract of the right ventricle may cause dulness in portions of the left second and third interspaces adjacent to the sternum. In such cases, as for instance in certain congenital lesions, dulness to the left of the sternum is not associated with a flat percussion sound over large areas of the sternum as is characteristic of pericardial effusion.

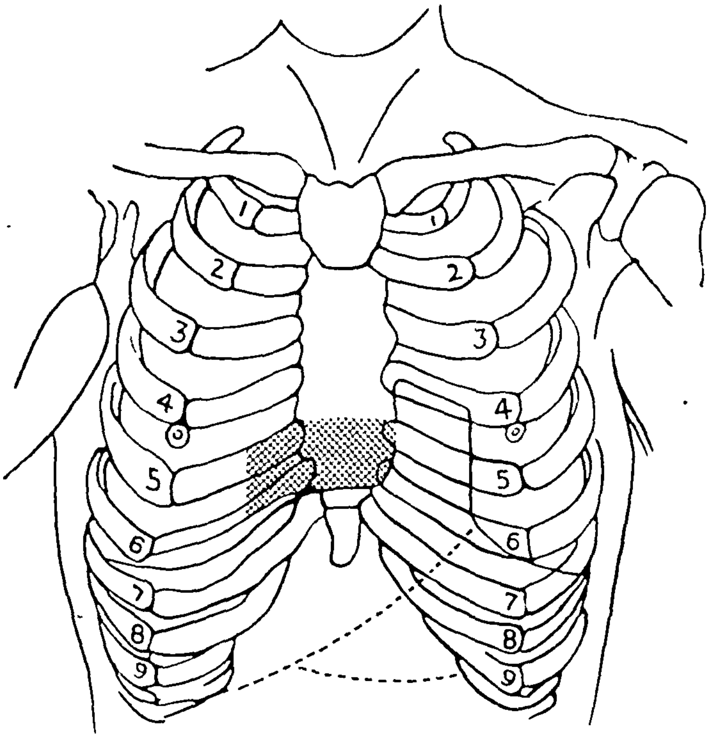

Fig. 3.—In presence of right heart failure and dilatation of right atrium and ventricle, small areas of percussion dulness (indicated by *cross-hatching*) are observed over lower portion of sternum and in fifth right intercostal space.

In rare cases, a huge left atrium or a giant right atrium may mimic the percussion findings of pericardial effusion. The former is invariably associated with a rheumatic lesion of the mitral valve; the latter occurs in rare instances of tricuspid stenosis of marked degree, or, it accompanies extreme tricuspid regurgitation or Ebstein's disease. These types of atrial dilatation can be readily excluded when evidence of rheumatic lesions of the mitral valve, a giant left atrium shown by barium swallow, tricuspid regurgitation, or Ebstein's disease is absent. In most instances, pericardial effusion is encountered as an isolated heart lesion. Hence, its differential diagnosis by way of percussion is rarely difficult.

Summary

Thirty-two cases of pericardial effusion were studied, and the differential diagnostic results from cardiac dilatation obtained by a single roentgenographic study and by percussion, respectively, were compared. A correct diagnosis was made in 13% (4 of 32 cases) on the basis of a single roentgenogram. The incidence of correct diagnoses rose to 58% (17 of 29 cases) when percussion findings were utilized for the diagnosis.

A simplified method of percussion was used which markedly reduced the subjective source of error. Instead of percussing the borders of the heart, utilizing "relative" percussion dulness, abnormal areas yielding a perfectly flat percussion sound were evaluated. The finding of a flat percussion note over the lower half of the sternum, sometimes extending upward as far as the level of the second costal cartilage, proved to be the leading sign in the diagnosis of pericardial effusion. Two other large areas of flat percussion sound were often observed: one in the left third intercostal space adjacent to the sternum; the other extending from the sternum to the right side between the third and sixth ribs.

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SUBCUTANEOUS FAT NECROSIS ASSOCIATED WITH ACUTE PANCREATITIS

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and
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The medical histories of three patients show the association of subcutaneous fat necrosis and polyarthritis in acute pancreatitis. The serum amylase levels were extremely high, reaching a peak two to three days after the appearance of the skin lesion. It is believed that lipase liberated from the pancreas acts on the involved fat tissue, changing the fat to fatty acid and glycerol which, being water-soluble, is carried into the lymphatics while fatty acids combine with calcium to produce insoluble soaps. The soaps make up the opaque plaques characterizing fat necrosis. These enzymatic and chemical reactions explain the fat necrosis and the hypocalcemia frequently seen in patients with acute pancreatitis.

Pancreatic and intra-abdominal fat necrosis is a common occurrence in acute pancreatitis. Less often, involvement of extra-abdominal sites is found, with fat necrosis of mediastinal, pericardial, pleural, periarticular, bone marrow, or subcutaneous fat tissue. During a period of 12 months, three cases of subcutaneous fat necrosis in association with acute pancreatitis were seen at the Veterans Administration West Side Hospital, Chicago.

Report of Cases

CASE 1.—A 45-year-old male truck driver was admitted to the hospital with a 10-day history of progressive weakness, anorexia, and dull midsternal chest pain unrelated to exertion but associated with belching and bloating after meals. His stools and urine were normal in color. He had lost 60 lb. (27.2 kg.) in body weight in the 18 months prior to admission and had noted intolerance to greasy foods. He admitted to heavy alcoholic intake and, in 1950, was hospitalized at another V. A. hospital, where he was treated for chronic alcoholism, Laennec's cirrhosis, and peripheral neuritis.

Physical examination revealed a cachectic man, in no acute distress, alert and oriented but having frequent eructations. The radial pulse rate was 120 per minute, blood pressure 110/85 mm. Hg, respiration rate 28 per minute, and oral temperature 100.6 F (38.1 C). His tongue was smooth and coated. The lungs were clear to percussion and auscultation. The heart was normal but for a sinus tachycardia. There was resistance to palpation in the midline at the epigastrium and in the right upper quadrant of the abdomen, extending 6 cm. below the right costal margin. The liver edge and spleen were not palpable. There was no abdominal tenderness. A brown-colored stool specimen gave a negative result to testing with guaiac.

Laboratory data included a hemoglobin level of 12.5 Gm.% and a hematocrit reading of 39%. The white blood cell count was 25,950 per cubic millimeter, with a differential count of 95% neutrophils, 3% lymphocytes, 1% monocytes, and 1% eosinophils. The platelet count was 348,000 per cubic millimeter. The bleeding time was 1½ minutes, the Lee White coagulation time 10 minutes, and the prothrombin time 15 seconds, with a control of 12 seconds. Serologic tests showed normal values: nonprotein nitrogen 21 mg.%, fasting blood sugar 237 mg.%, serum amylase 462 Somogyi units (milligram glucose per cent), phosphorus 2.7 mg.%, calcium 7.8 mg.%, total protein 5.7 Gm.%, albumin 3.1 Gm.%, and globulin 2.6 Gm.%. The alkaline serum phosphatase level was 8.4 units per 100 cc. (Bodansky), thymol turbidity 0.6 units, and sulfobromophthalein retention 27% in 45 minutes. The total level of serum bilirubin was 0.9 mg.%, serum potassium level 4.2 mEq. per liter, serum sodium level 136 mEq. per liter, and serum chloride level 88 mEq. per liter. A roentgenogram of the chest revealed calcifications in both hili. The heart was normal in size. Scout films of the abdomen revealed calcifications in the region of the pancreas. The electrocardiogram revealed a sinus tachycardia and an A-V conduction defect.

The patient was treated initially with a soft diet, supplemental vitamins, aluminum hydroxide (Amphogel), atropine, and bed rest. His temperature ranged between 100 and 102 F (37.8 and 38.9 C). On the second day after admission he developed nodular, tender, erythematous lesions of the skin on both legs and on both hands and forearms. These

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were associated with erythema and tenderness of both ankles. The clinical diagnosis was erythema nodosum, and salicylate therapy was instituted. Although the rash faded rapidly, the serum amylase level remained elevated. Two weeks after admission he became lethargic, disoriented, and exhibited unusual behavior suggesting impending hepatic coma. He was then started on therapy with intravenous administration of fluids, calcium gluconate, and hydrocortisone. Restraints and sedation were necessary. A diagnostic lumbar puncture revealed normal dynamics, and cell studies and electrolyte studies yielded normal results. The patient's condition improved and he became rational and oriented. A roentgenogram of the chest taken at this time revealed a massive left pleural effusion. The fluid on aspiration was straw-colored, and the result of amylase determination was 13,350 Somogyi units.

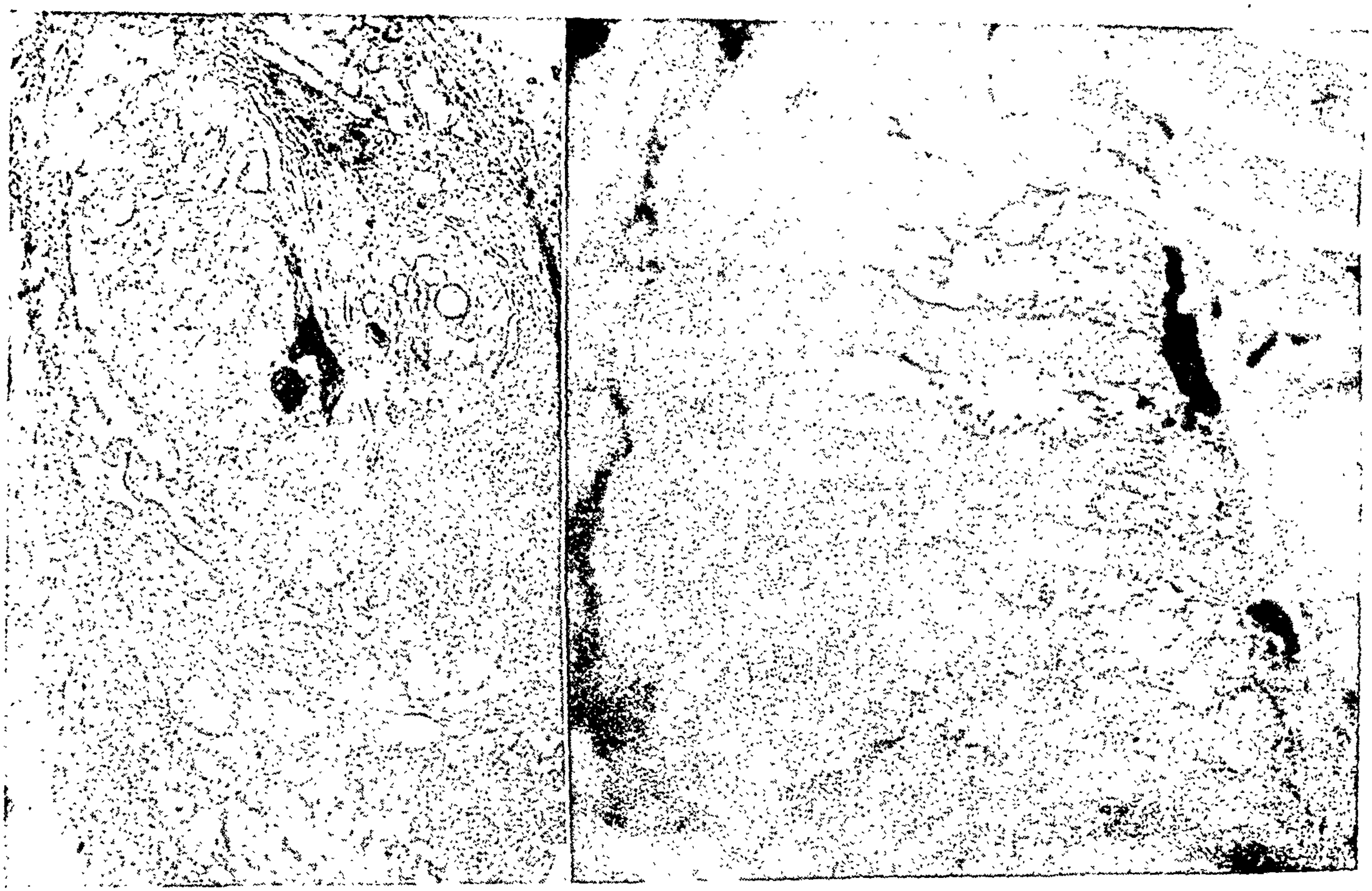

Fig. 1. (case 1).—Association between subcutaneous fat necrosis and acute pancreatitis. *Left,* microscopic section of subcutaneous tissue from malleolar region, showing fat necrosis surrounded by calcification, inflammation, and fibrous tissue. *Right,* photograph of left pleural cavity, showing subpleural fat necrosis.

An exploratory laparotomy revealed multiple intra-abdominal abscesses in the properitoneal fat of the epigastrium and in the retroperitoneal fat of the left upper quadrant, with diffuse fat necrosis. Drainage was accomplished. His postoperative course was complicated by hypotension and toxicity. When cut-downs were made at the medial malleolar areas, yellowish necrotic subcutaneous tissue exuded from the skin incisions on both the right and left side.

The patient's course was progressively downhil and he died two months after admission. At autopsy, the previously noted necrotic subcutaneou fatty tissues of both ankle regions showed fa necrosis on microscopic examination (fig. 1, *left*) The left pleural cavity contained 300 cc. of clea fluid, and the subpleural intercostal tissues reveale fat necrosis (fig. 1, *right*). The right pleural cavit showed fibrous adhesions and 200 cc. of fluid. N subpleural fat necrosis was present on the right The peritoneal cavity did not contain fluid but ha many fibrous adhesions linking the right lobe of th liver to the omentum and transverse colon. Th omental, mesenteric, and peripancreatic fat tissues showed extensive fat necrosis similar to that seen at the time of exploratory laparotomy. The pancreas weighed 90 Gm. (3.5 oz.) and showed acute hemorrhagic pancreatitis superimposed over chronic pancreatitis, with multiple pseudocysts measuring up to 3 cm. in diameter. There was minimal fatty cirrhosis of the liver. The heart revealed a healed myocardial infarct of the posterior lateral wall of the left ventricle.

Case 2.—A 39-year-old man entered this hospital with acute upper abdominal pain of several days' duration. The pain, sharp in nature, occurred two hours after eating and was followed by nausea and vomiting. His medical history revealed a heavy alcoholic intake for many years and nausea with vomiting after meals, for three months prior to admission. There was no weight loss, hematemesis, diarrhea, tarry stools, or melena. He had received treatment for pulmonary tuberculosis from 1951 to 1954 and his case was now considered arrested.

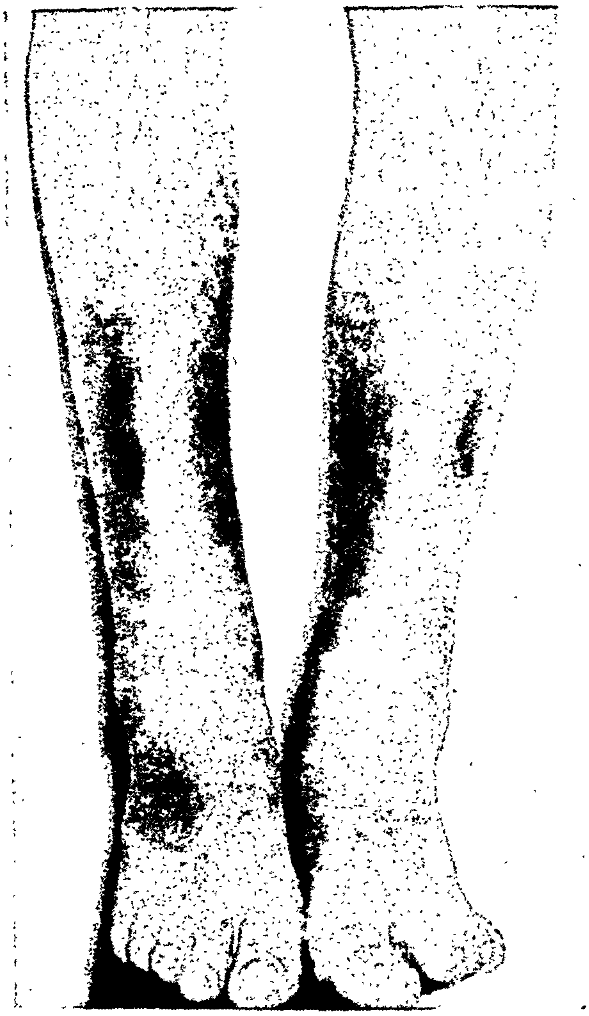

Fig. 2. (case 2).—Photograph of lower extremities, showing erythematous nodular rash with swelling of both ankles.

Physical examination revealed an icteric, well-developed, alert, obese man with mild abdominal distress. The pulse rate was 99 per minute, blood pressure 132/85 mm. Hg, oral temperature 100.8 F (38.2 C), and respiration rate 24 per minute. His heart and lungs were normal. His abdomen was protuberant, with a slightly movable, tender mass about 15 cm. in diameter just to the left of the midline above the umbilicus. The liver edge was 14 cm. below the right costal margin. The spleen was not palpable. Laboratory data on admission included a hemoglobin level of 14.5 Gm.% and a hematocrit reading of 47%. The white blood cell count was 10,000 per cubic millimeter, with a differential count of 85% neutrophils, 9% lymphocytes, 1% monocytes, and 5% stab forms. The blood urea nitrogen level was 17 mg.%, fasting blood sugar 112 mg.%, and alkaline phosphatase level (Bodansky) 2.5 units per 100 cc. The direct serum bilirubin level was 7.9 mg.%, indirect serum bilirubin 13.3 mg.%, cephalin flocculation 3+ at 24 hours and 4+ at 48 hours, and thymol turbidity 1.6 units. The serum amylase level on admission was 165 Somogyi units. Findings of a roentgenogram of the chest and a barium enema were normal. Results of a gallbladder series were normal, without evidence of stones. An upper gastrointestinal roentgenographic study showed a widened duodenal sweep, with extrinsic pressure on the gastric antrum.

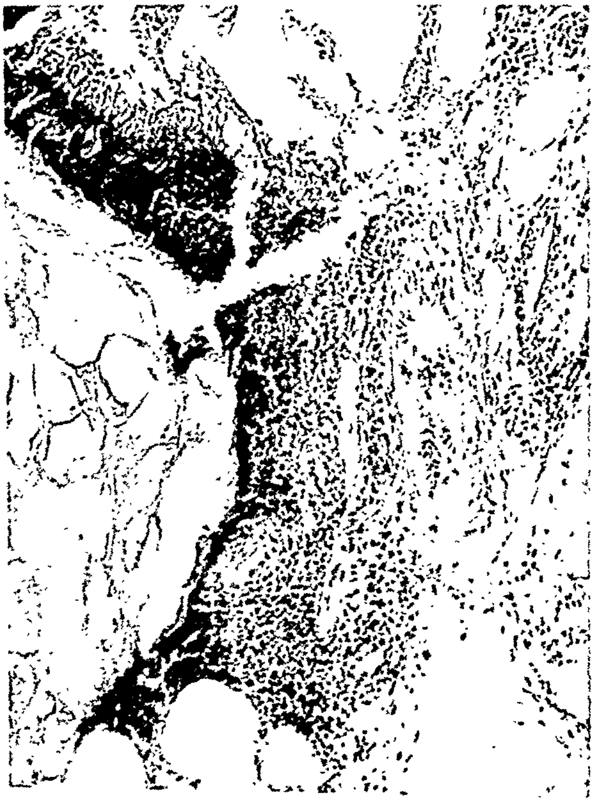

Fig. 3. (case 2).—Microscopic section of skin biopsy, showing necrosis of subcutaneous fat tissue surrounded by fibrous and inflammatory tissue.

The initial treatment consisted of gastric suction, intravenously given fluids, and administration of atropine and meperidine hydrochloride. On the third day he developed multiple tender, nodular, erythematous lesions over both lower extremities (fig. 2) and both ankles became swollen. These nodular lesions varied in size from a few millimeters to 3 cm. in diameter and were confluent in several areas. A punch biopsy specimen revealed subcutaneous fat necrosis (fig. 3). The erythema, edema, and pain persisted in the nodular areas for 5 to 6 days, followed by a gradual resolution of the lesions and the pain over the next 10 days. The epigastric mass persisted for three weeks and then slowly resolved. The patient is now well and asymptomatic.

CASE 3.—A 37-year-old man was admitted because of upper abdominal pain of six days' duration. He had had severe, continual vomiting for three days prior to admission. There was a history of heavy alcoholism, and he had been drinking excessively for two weeks prior to the onset of symptoms. The medical history revealed two episodes of pain similar to the present episode, but of less intensity and shorter duration.

Physical examination revealed a well-developed, dehydrated man with abdominal distress, somewhat relieved by sitting up. The pulse rate was 74 per minute, blood pressure 140/90 mm. Hg, and oral temperature 98.8 F (37.1 C). The abdomen was flat and soft, with hypoactive bowel sounds. There was tenderness in the left upper quadrant and epigastric region. There were no rebound tenderness and no palpable masses. The liver and spleen were not palpable.

Laboratory studies revealed a hemoglobin level of 13 Gm.% and a hematocrit reading of 43%. The white blood cell count was 20,100 per cubic millimeter, with a differential count of 72% neutrophils, 13% lymphocytes, 2% monocytes, 3% eosinophils, 1% basophils, 8% stab forms, and 1% juvenile cells. Urinalysis revealed a content of 2+ albumin, 4+ acetone, and a sediment with numerous white and occasional red blood cells. The serum amylase level was 415 Somogyi units. Cephalin flocculation was normal, thymol turbidity 0.4 units, alkaline phosphatase level 2.8 units per 100 cc., fasting blood sugar 123 mg.%, and sulfobromophthalein retention 11% in 45 minutes. The calcium level was 9.5 mg.% and that of phosphorus 2.9 mg.%. Results of roentgenographic studies of the chest and abdomen were normal. An upper gastrointestinal barium study revealed a soft tissue mass displacing the stomach anteriorly.

A diagnosis of acute pancreatitis was made on admission. A nasogastric tube was inserted and continuous gastric suction started. Intravenously given fluids, promazine hydrochloride, and atropine were also administered. The patient's condition improved rapidly and he was completely asymptomatic on the sixth day, when a questionable fulness was noted in the left upper quadrant. A clear liquid diet was started on the eighth day. Recurrent epigastric pain was noted on the ninth day. No mass was denoted at this time. Gastric suction was reinstituted and the patient again responded rapidly. On the 17th postadmission day, both ankles and the distal anterior tibial areas became swollen, tender, warm, and erythematous, with diffuse subcutaneous nodularity. A skin biopsy specimen revealed subcutaneous fat necrosis. At this time the serum amylase level was 1,055 units. The initial therapeutic regimen was instituted. The swelling and erythema gradually subsided over the next several days. The patient became asymptomatic, but a cystic mass developed in the epigastrium and in the left upper quadrant. This was thought to represent a pseudocyst of the pancreas. The patient's course was uncomplicated and the mass slowly resolved.

Comment

The association of fat necrosis with acute pancreatitis is a well-known entity. It is believed that lipase liberated from the pancreas acts on the involved fat tissue, changing the fat to fatty acid and glycerol which, being water soluble, is carried into the lymphatics while fatty acids combine with calcium to produce insoluble soaps. The soaps make up the opaque plaques characterizing fat necrosis. These enzymatic and chemical reactions explain the fat necrosis and the hypocalcemia frequently seen with acute pancreatitis.

Fat necrosis of the bone marrow in acute pancreatitis has been reproduced experimentally by the intravenous injection of lipase.[1] A case showing cerebral demyelinization and focal visceral lesions of the myocardium, adrenals, and ovaries, associated with acute hemorrhagic pancreatitis was reported by Vogel,[2] who hypothesized that these lesions had been caused by circulating pancreatic enzymes. Lynch[3] reported a case of nephrosis in a patient with acute pancreatitis which he believed to be due to ischemia secondary to fat embolism. Lesions of the lungs, heart, and brain in this case were likewise attributed to fat embolization. Edmondson and Fields[4] also have described this process.

Pleural effusion with pancreatitis is not infrequent and is usually left-sided. The lymphatic vessels probably play a role in the transmission of lipase to both the thoracic and abdominal linings. This has been clearly shown by the experimental work of Perry,[5] who gave intraperitoneal injections of pancreatin and fine graphite particles to white rats. Autopsy specimens showed fat necrosis to be closely associated with lymph channels delineated by the graphite. Reports of amylase determinations of pleural fluid are not readily found in the literature. The highest reported value found on review of the literature was 800 amylase units.[6] Opie[7] was able to reproduce peripancreatic fat necrosis by ligating the pancreatic ducts in cats. He also produced subcutaneous fat necrosis by transplanting the pancreatic ducts of cats into their abdominal wall. The mode of activation of the pancreatic enzymes is still unexplained.

Subcutaneous fat necrosis with pancreatitis was originally described by Chiari[8] in 1883, and next reported by Hansemann[9] in 1889. Review of the literature shows no reports of this entity until those described by Zaaijer[10] in 1935, by Blauvelt[11] in 1946, by Scarselli[12] in 1954, and more recently by Kushner and Szanto[13] in 1958. The resemblance of the skin lesions in Blauvelt's case to those of erythema nodosum was pointed out, the involvement being predominantly of the skin of the legs and arms. The case reported by Scarselli demonstrated marked hemorrhagic and necrotic features of the involved skin of both the trunk and extremities, associated with generalized arthralgia. In the case reported by Kushner and Szanto, polyarthritis and fever were prominent and involvement of the trunk and extremities was again seen. The arthritis was shown to be secondary to necrosis of the periarticular fat tissue.

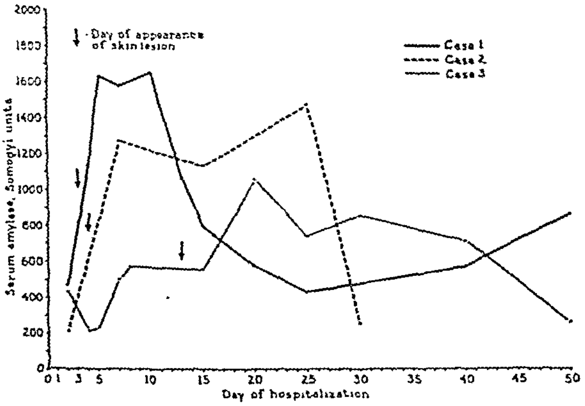

Fig. 4.—Graph of serum amylase levels, showing their prolonged elevations and time of onset of skin lesions.

In 1959, Mayoral and associates[14] reported a case of subcutaneous fat necrosis associated with pancreatitis and portal cirrhosis. They referred to five cases of subcutaneous fat necrosis, each associated with carcinoma of the pancreas. Carcinoma was not present in any of our cases.

Our own cases here reported clearly reveal the association of subcutaneous fat necrosis and polyarthritis in acute pancreatitis. It is interesting that the serum amylase levels were extremely high and remained high for a long period (fig. 4), reaching a peak two to three days after the appearance of the skin lesion.

Summary

The association of subcutaneous fat necrosis with acute pancreatitis is not as infrequent as the number of reports in the literature would indicate. In three cases here reported, serum amylase levels were grossly elevated and remained high for a considerable period. The clinical manifestations of this entity suggest more familiar pathological states, such as cellulitis, periarteritis nodosa, acute thrombophlebitis, allergic phenomena, or trauma. A greater clinical awareness of this entity will facilitate the proper diagnosis.

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J.A.M.A., June 18, 1960

HEMORRHAGE AND TRANSFUSION AS THE MAJOR CAUSE OF CARDIAC ARREST

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Analysis of 157 cases of cardiac arrest led to the conclusion that in 50 of these the sole cause was massive transfusion of hyperpotassemic bank blood. The bank blood rapidly administered to these patients contained an average total of 77.7 mEq. of potassium. In an additional group of 18 of the 157 cases, transfusion contributed to the production of cardiac arrest. Serum potassium concentrations increase progressively in bank blood, and hemorrhage increases the susceptibility of the body to potassium. These considerations are of fundamental importance in the steps here recommended for avoiding cardiac arrest and in treating it when it occurs.

Over the past decade, there has been a puzzling increase in the frequency of cardiac arrest. This increased incidence has occurred despite the high degree of perfection achieved in the science of anesthesiology. Cardiac standstill is occurring more often even in those institutions where anesthesiologists are actually practicing physiologists. Without further information about the etiology of cardiac arrest, little can be done to prevent its occurrence.

Our attention was recently focused on blood transfusion as an etiological factor. We noted that cardiac arrest occurred in several patients after massive transfusions.[1] The arrests occurred some time after hemorrhage had been controlled and the patient did not appear to be in jeopardy. In each of these early cases, a transfusion of bank blood was being given to the patient at the time cardiac arrest occurred.

The serum potassium concentration rises progressively during the storage of blood. The extent of this increase varies considerably with the way that the blood is handled. In our hospital, all blood is purchased. The blood is collected in another area of the United States and transported to New York. It is again transported to the hospital on request. For these reasons, the blood at our hospital may be subject to greater mechanical stresses than at some hospitals which operate their own blood banks. The increase in the plasma potassium level of stored bank blood is illustrated in figure 1. Notice how potassium continually escapes from refrigerated erythrocytes during storage of blood. At the end of two weeks, levels as high as 24 mEq. per liter may be reached.

Hypovolemic shock increases the susceptibility of animals to cardiac arrest induced by the intravenous injection of potassium salts.[2] Administration of digitalis helps restore resistance to potassium infusions. By comparison with normal requirements, only one-third of the quantity of potassium is required to produce fatal cardiac arrest during hemorrhagic hypotension (fig. 2). Hemorrhagic hypotension is an intense stimulus for the liberation of epinephrine. The action of epinephrine causes glycogenolysis in the liver resulting in a release of glucose into the blood. As glucose is released, potassium is simultaneously liberated. This is the reverse of the situation prevailing in hypopotassemia induced during insulin therapy for diabetic coma (fig. 3, *left*). In this circumstance, glucose is deposited in the liver and with it, potassium; hence, hypopotassemia results. During hemorrhage, glycogenolysis tends to produce hyperpotassemia primarily because hemorrhage itself is a stimulant to the sympathetic nervous system (fig. 3, *right*).

Carbon dioxide accumulation is another intense stimulus to epinephrine secretion and similarly mobilizes potassium from the liver. In adrenalectomized animals, carbon dioxide fails to release potassium and glucose from the liver.[3] The liberation of potassium from the liver and the simultaneous intravenous injection of hyperpotassemic bank blood selectively raise the potassium concentration of the venous blood returning to the heart. This may not be apparent when samples of peripheral blood are obtained from the antecubital vein. When cardiac arrest was induced in dogs by the injection of potassium during hemorrhagic hypotension, the cardiac potassium level was almost three times that found in the peripheral blood samples obtained from a leg vein. The role of potassium as a causative agent in cardiac arrest may similarly be undetected in the operating room when arrest occurs during rapid transfusion of hyperpotassemic bank blood. Potassium injected into the blood stream and potassium released from the liver reach the heart first. The arterial blood leaves the heart and has an opportunity to equilibrate with the extracellular fluid before reaching the venous side of the circulation. Burch [4] has shown that the equilibration

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of radioactive sodium and potassium with extravascular fluid spaces occurs at once. The central blood supply has no opportunity to lose its potassium and hence there is a disparity between the concentrations in peripheral and in cardiac blood. This disparity between central and peripheral potassium concentrations was first noted by Scudder and Zwemer[5] in their experiments with subjects in hemorrhagic shock. Stewart's experiments proved that anoxia of the liver, even in the absence of the adrenal glands, may cause a release of potassium sufficient to induce first-stage heart block in the experimental animal.[6] Although potassium is released from all tissues during anoxia, the greatest release occurs from the liver. The endogenous potassium release coupled with the rapid transfusions of hyperpotassemic bank blood may thus lead to cardiac arrest without its being detected in peripheral blood potassium levels.

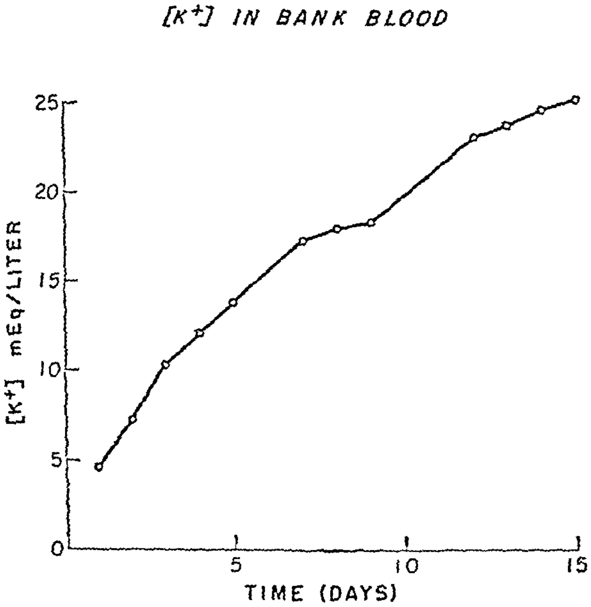

Fig. 1.—Concentration of extracellular potassium plotted against time (published with permission of *Surgery, Gynecology & Obstetrics*).

Our experiments with animals substantiated the theory that quantities of potassium which might be contained in hyperpotassemic bank blood could induce cardiac arrest during hypotension, but the major problem remained to investigate clinical cases of cardiac arrest to determine just how frequently transfusion might be the etiological agent. The literature does not implicate this as a cause for cardiac arrest.

The following report deals with an analysis of 157 cases of cardiac arrest drawn from the hospital records at Brooklyn Veterans Administration Hospital, Manhattan Veterans Administration Hospital, Bronx Veterans Administration Hospital, and Kings County Hospital over the past seven years. In analyzing the causes of death, it became apparent that some cases were diagnosed as cardiac arrest but in reality represented end-stages of cardiac disease in medical patients. Such cases were omitted from the study even though cardiac massage was occasionally performed on patients in the wards. All cases occurring in infants under 1 year of age were also omitted. There were a number of such cases in which asphyxia or congenital malformations played a prominent role. About 58 cases were excluded for these reasons. Some cases were reported not as cardiac arrest but as hemorrhage, and therefore all deaths from hemorrhage were reviewed to preclude omissions of cases of cardiac arrest associated with hemorrhage. All causes of death occurring in the operating room or within 24 hours postoperatively were scrutinized as well.

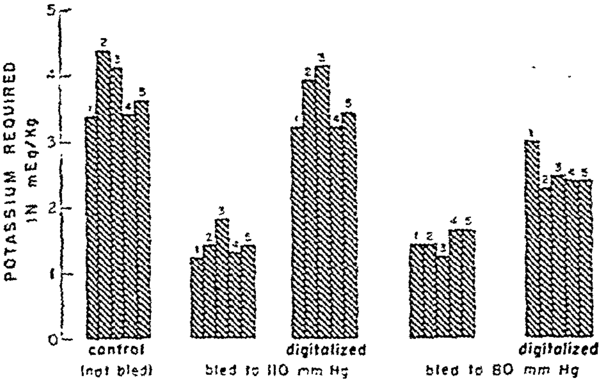

Fig. 2.—Each bar indicates amount of potassium per kilogram of body weight required to produce fatal cardiac arrest in dog. Lethal dose decreases by one-third during the simple hemorrhage with blood pressure reduction to 120 mm. Hg; further increase in sensitivity to injected potassium occurs with hemorrhage and blood pressure reduction to 80 mm. Hg (published with permission of *Surgery, Gynecology & Obstetrics*).

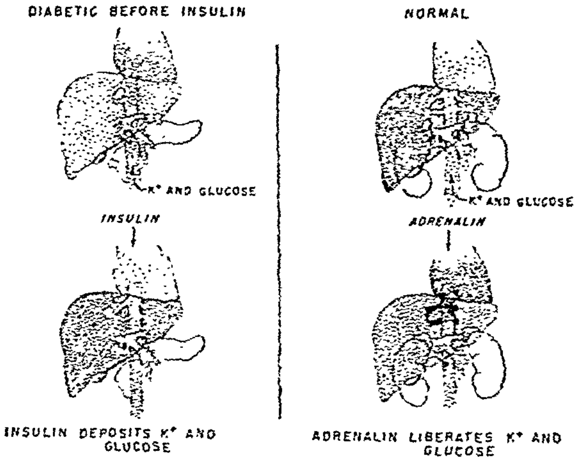

Fig. 3.—Potassium molecules depicted as dots in diagrams. *Left*, before insulin therapy, liver concentration of glycogen and potassium is low; plasma potassium concentration may be normal or high. Insulin therapy causes deposition of potassium and glycogen in liver and induces serum hypopotassemia. *Right*, epinephrine causes liberation of glucose and insulin from liver, with serum hyperpotassemia greatest in blood returning to heart; after leaving heart, equilibration with extracellular fluid potassium occurs.

The diagnosis of cardiac arrest was made by electrocardiogram, sudden cessation of major pulsation during surgery, or direct visualization of the heart. A total of 157 cases remained in the survey for analysis.

Results of Study

An attempt was made to determine the major etiological factor in each case. The cause of cardiac arrest together with the number of patients involved is listed as follows: primary transfusion, 50; primary cardiac condition, 28; primary cause unknown, 26; multiple etiology, 21; airway obstruction, 19; bronchoscopy and esophagoscopy, 7; pulmonary emboli, 4; neurological condition, 2; total, 157. In the entire number of patients, 50, or about one-third, of the cases of cardiac arrest could be attributed solely to the transfusion of blood. In an additional 18 cases (11%), it was found that blood transfusion played a contributory role in the production of the cardiac arrest. They were not included with the primary transfusion group because some of these patients had other disease which also was contributory. The analysis of the other factors in these cases, with the number of patients involved is as follows: airway obstruction, 1; primary cardiac condition, 8; unknown etiology, 4; multiple etiology, 5; total, 18. We were startled to find that transfusion played a major etiological role in cardiac arrest in 68 of the 157 cases (44%). The following discussion is limited to those cases in which transfusion was considered the sole cause of cardiac arrest.

The rate of administration might be important, since rapid transfusion would place a sudden potassium burden on the body. In cases in which it was possible to obtain information about the rate of blood administration, or to calculate the rate from the number of pints that were administered over a given period, it was found that over 500 cc. of blood was administered in less than 15 minutes in 19 cases. In those patients in whom transfusion was the only cause of cardiac arrest, more than 2,000 cc. of blood was used during operation. Seven patients received 2,000 to 3,000 cc. of blood; 43 received more than 3,000 cc.; and 31 received more than 4,500 cc. Twelve of 43 patients, or 29% of those receiving 3,000 cc. or more of blood, were resuscitated. The vital signs prior to cardiac arrest were noted in order to determine whether these signs disclosed any indication of the impending disaster. The blood pressure dropped in 22 patients. In 12 patients the drop was sudden, but in 8 patients the drop was slow. The blood pressure rose immediately prior to cessation of the heart beat in nine patients. Blood pressure showed no change prior to the cardiac arrest in 14 patients; it was increased in 9 and slowed in 7.

Vital signs cannot be relied on to indicate the extent of hemorrhage.[7] Even though vital signs give no measure of the blood loss or warning of the imminent disaster, these were relied on to indicate the status of the cardiovascular system. This, unfortunately, illustrated the reliance placed on these variable physical signs and the little attention given to actual measurement of blood loss. Blood loss determinations were made in only 13 of the patients, as follows. Gravimetric determinations were obtained in 10 patients; hemoglobin concentrations were not measured in any patients; no patients were weighed; dye dilution tests were performed in two patients, and conductivity was measured in one patient. In 30 patients the blood loss was estimated and in some cases even this was not done.

The anesthetic agent varied in the entire group of 157 patients, and in most cases a mixture of several anesthetic agents was used. Only five of the patients had spinal anesthesia, while in the rest surgery was performed under general anesthesia. Of the 50 patients in whom transfusion played the major etiological role in cardiac arrest, 25 received cyclopropane. We do not know whether this has significance, since this anesthetic agent is used frequently in this geographical area.

In some cases the surgeon failed to describe the condition of the heart, and the distinction between cardiac arrest and fibrillation was not made in 16 patients. The myocardium was described as being in arrest in 34 of the 50 patients and description of a flabby myocardium was recorded in 4 patients. In no patient was the myocardium found to be contracted. In 2 of the 50 patients who received transfusions, the heart was described as fibrillating initially. Fibrillation occurred after massage in 8 of the 50 transfusion-arrest patients. It is interesting that seven of these eight patients received cyclopropane. Six of the eight had received epinephrine to resuscitate them. Defibrillation was effective in only one patient, while in eight patients it was considered ineffective. Successful resuscitation occurred in 12 patients with varying periods of massage of from 5 minutes to 1 hour and 10 minutes.

In those patients in whom resuscitation was unsuccessful, the length of cardiac massage varied from 10 minutes to two and one-half hours. Five of the resuscitated transfusion-arrest patients were normal after resuscitation. The rest of the patients either incurred permanent damage or died. Many drugs were used to effect contraction. Pure epinephrine was used in 9 of the 50 patients who received transfusion and was mentioned in 6 cases as not effectively altering the contractility of the heart. In 13 of the patients who received transfusions, epinephrine and calcium were given simultaneously. These medicaments were mentioned as effective in four cases. In five cases digitalis was given and was said to be effective in three cases. Although digitalis was seldom given, it seemed to be the most effective of those drugs which were administered. Thirty-eight of the 50 cases of transfusion arrest occurred in the operating room, 9 occurred in the recovery room, and 3 occurred on the wards.

The average total estimated potassium dose administered to the patient in the form of hyperpotassemic blood was calculated from the average age of blood and the amount of blood given, as shown in figure 1. In these calculations, it must be remembered that 120 cc. of acid-citrate-dextrose (ACD) solution is present in each bottle, bringing the proportion of extracellular fluid in this blood from 55 to 63%. In those patients in whom cardiac arrest was produced by transfusion alone, the average dose of potassium was 77.7 mEq. The ages of the transfused blood in these cases are shown in the table. In those patients in whom the transfusion of blood was contributory to the cardiac arrest, the total dose of potassium given was 57 mEq.

Report of Cases

Case 1.—A 56-year-old woman entered Kings County Hospital with a complaint of hemoptysis. Examination revealed an infiltrated process involving the right middle and lower lobes of the lung. When the lesion failed to respond to therapy in one month, an exploratory thoracotomy was performed, with nitrous oxide and a barbiturate preparation used as anesthetic agents. The patient was considered a good operative risk. At operation the middle and lower lobes were found to be hard and rubbery. There were numerous firm lymph nodes situated on the superior vena cava and on the inferior and superior pulmonary veins, as well as on the pericardium. A frozen section of one of these nodes revealed chronic inflammation. At the beginning of the operation it was decided to remove the middle and lower lobes, but when the dissection was begun, the pulmonary artery was seen to be lacerated. Profuse bleeding was encountered. The patient received 10 pt. of blood in the operating room. The average age of the blood was 18.3 days. The blood was pumped because of the rapidity and extent of the blood loss. Twice during the procedure no blood pressure could be obtained, and on examination the heart was noted to be in cardiac arrest. The heart was massaged and epinephrine and calcium were given, and the beat returned with force and vigor. The rent in the artery was finally sutured and the patient was returned to the ward without further surgery. The lung was resected successfully at a later date.

Age of Bank Blood Administered in Cases of Transfusion Arrest

Age of Blood*	
Days	Pints, No.
0- 3	62
4- 6	63
7- 9	63
10-12	64
13-15	83
16-18	49
19-21	21
22-24	18
25-27	14
28 and over	4

* Average 11 days.

Case 2.—A 59-year-old man was admitted to Kings County Hospital with abdominal pain and a systolic blood pressure below 100 mm. Hg of 12 hours' duration. He had had two myocardial infarcts substantiated by electrocardiogram but no evidence of recent damage could be detected. An 8-in. pulsatile mass, occupying the entire right side of the abdomen, was palpated. Blood transfusions were started and he was taken to the operating room for resection of an aortic aneurysm. At operation an aneurysm was rapidly identified and proximal ligation was performed. Up to this point the patient was given a transfusion of 3,000 cc. of blood averaging 18.6 days old. This blood was given over less than two hours. The patient's blood pressure began to drop even though the replacement was considered adequate, and a full and distended vena cava was observed. Shortly thereafter the anesthetist could detect no pulse and an emergency thoracotomy was performed. The heart was noted to be dilated and tense in the pericardium. Massage was carried on by one team while the abdominal surgery was completed by a second team. During this two hours a normal spontaneous rhythm was maintained with use of calcium and epinephrine, defibrillation, and massage. At the end of this time the myocardium felt mushy and the pupils became fixed and dilated. The operation was terminated at this point. Although the blood loss had been controlled, the veins remained distended, and cardiac action could not be restored. A total of 4,500 cc. of blood (average age, 18.6 days old) was given. Blood loss was determined by gravimetric procedure and was 5,500 cc. at the conclusion of surgery.

Case 3.—This case illustrates cardiac disease in which blood transfusion played a role in mortality. A 36-year-old woman was admitted to Kings County Hospital with a history of inactive rheumatic heart disease with mitral stenosis. Because of the patient's increasing dyspnea, it was decided to perform a mitral commissurotomy. She was considered a good surgical risk. She received atropine and meperidine (Demerol) hydrochloride before operation, and the anesthetic agents were nitrous oxide and oxygen combined with thiopental. Blood loss was determined gravimetrically. Before performance of a mitral commissurotomy was attempted, hemorrhage from a hole in the left auricle occurred. She was given a transfusion of 6,000 cc. of blood (average age, 16.1 days). The blood was pumped rapidly. Cardiac arrest occurred and the heart became flabby and distended. Cardiac massage was not effective in restoring heart action even though the hole in the auricle had been repaired.

Case 4.—This case illustrates proper balancing of blood loss and blood replacement. A 37-year-old man was admitted to Brooklyn Veterans Administration Hospital with a 14-month history of pulmonary tuberculosis. The lesion involved the right upper lobe, with cavitation and a decrease in the volume of the lobe. The patient received double antibiotic therapy. No organisms were recovered from the sputum two months after the initiation of this therapy, however, there remained a residual cavity with extensive fibrosis of the right upper lobe after six months. Elective surgery was performed, consisting of the removal of the diseased right upper lobe. Surgery and the postoperative course were uneventful (fig. 4). Blood replacement was balanced with blood loss and the patient never became hypovolemic, nor did the blood pressure or pulse rate vary considerably. This contributed to the uneventful postoperative recovery.

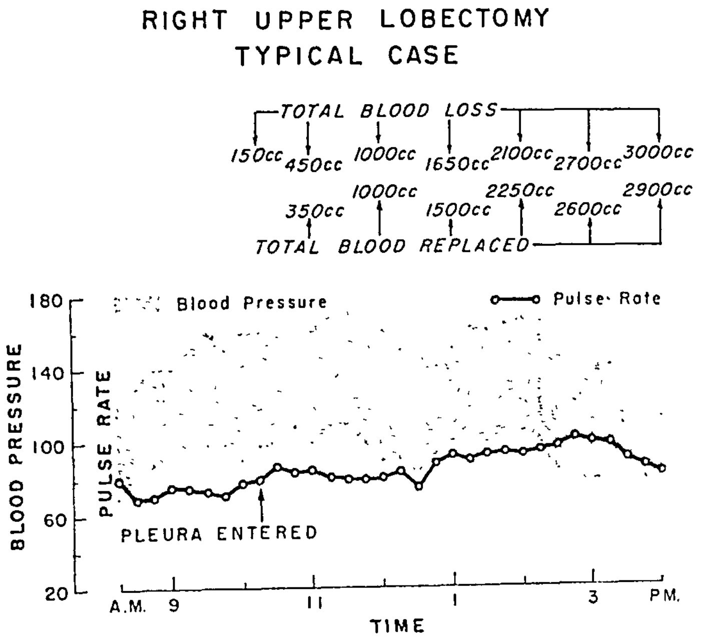

Fig. 4.—Illustration of proper operative matching of blood loss to blood replacement. At no time does patient ever become hypovolemic, and blood pressure and pulse rate never vary. Postoperative hemoglobin concentrations remain within normal range (published with permission of *The Journal of Thoracic and Cardiovascular Surgery*).

Comment

Potassium intoxication during blood replacement from hemorrhage was the major cause of cardiac arrest in 157 patients. Accurate measurement of blood loss has not received the proper attention it deserves because the relationship between blood replacement and cardiac arrest has not been apparent. It is essential that blood loss be monitored continuously and instantaneously during the course of surgery entailing exchanges so that the patient does not develop either hypovolemia or hypervolemia. Replacement must parallel the amount lost. It is hazardous to allow the patient to become so hypovolemic that the blood pressure falls. Then it will be necessary to transfuse bank blood by rapid pumping. If hemorrhagic hypotension is avoided, anoxia and epinephrine secretion will not occur and potassium liberation from the liver will be prevented. The measurement of blood loss at the operating table is simplified by use of a blood-loss monitor (fig. 5) which operates on the conductivity principle.[8]

If hypovolemic animals are infused with hyperpotassemic blood, the serum potassium concentration will rise progressively if the animal is maintained in a hypovolemic state, even though the blood pressure and pulse rate are normal and the hypovolemia is only mild.[9] Dogs with normovolemia and moderate hypovolemia were bled 100 cc. and loss of blood due to hemorrhage was simultaneously replaced with 100 cc. of hyperpotassemic bank blood. Ten such bleedings and retransfusions were performed over a period of one and one-half hours to simulate operative bleeding and replacement with bank blood. Potassium concentration builds up rapidly in hypovolemic dogs even though their blood pressures have undergone no change. The ability of the normovolemic animal to maintain a low serum potassium concentration while receiving large amounts of potassium in infusions indicates the efficiency of the renal removal mechanisms (fig. 6). Hypovolemia in addition to anesthesia and hypotension markedly depresses renal function, rendering the animal more susceptible to potassium intoxication from repeated small injections of potassium. The best method to protect the patient from potassium intoxication during operation is to maintain the blood volume at the normovolemic level.

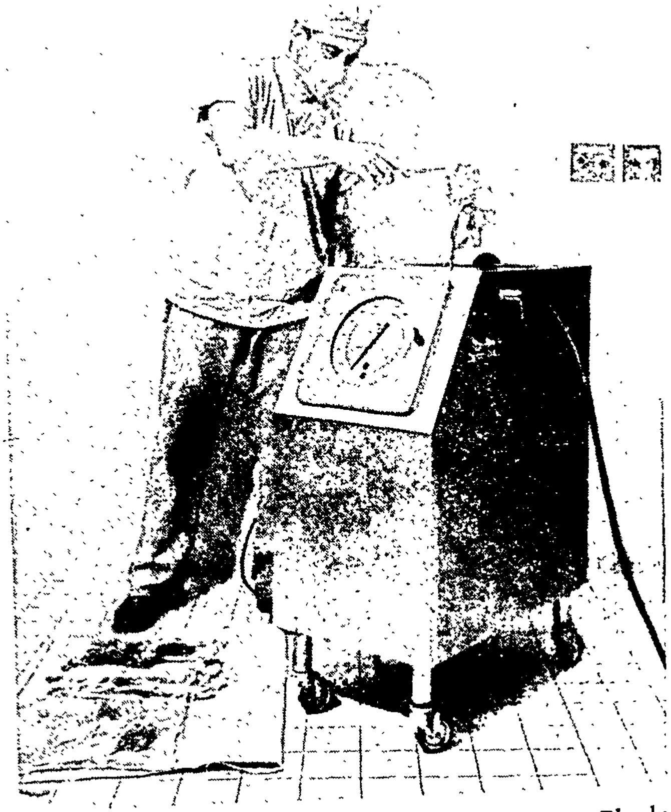

Fig. 5.—"Blood loss monitor" shown in actual use. Bloody laparotomy pad is being dropped into open tub; suction from operative field is connected to side of instrument. Total blood loss is immediately indicated by pointer on dial face.

In acute hemorrhage and in hemorrhagic shock, the venous pressure always falls.[10] Late in hemorrhagic shock, the venous pressure may rise; the exact cause of this is unknown, although it may be a manifestation of potassium toxicity. In our experimental work we have found that the blood pressure falls and the venous pressure rises dramatically in normovolemic dogs infused with toxic quantities of potassium. During hemorrhagic hypotension, the rise in venous pressure and fall in blood pressure can be more easily induced with smaller doses of potassium. The rise in venous pressure may be the only clue to the impending potassium intoxication. In case 2, the rise in venous pressure most certainly was due to potassium intoxication, since uncomplicated hemorrhagic hypotension would have lowered the venous pressure. In this case, as in others, the veins were described as being distended. The venous pressure fails to be a good index of the extent of hemorrhage when large quantities of potassium are being infused, since the venous pressure may rise under these circumstances even when replacement has been inadequate.

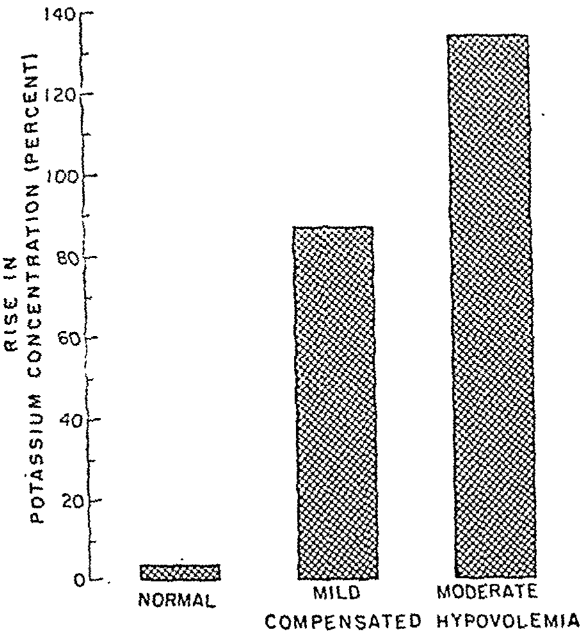

Fig. 6.—Chart representing dogs with normovolemia and moderate hypovolemia bled 100 cc. Serum potassium values are shown at end of experiment and expressed as percentages of normal values (published with permission of *Surgery*).

Contrary to the opinion of others,[11] the venous or right auricle pressure does not indicate the status of the blood volume and the adequacy of blood replacement. During resuscitation from cardiac arrest induced in dogs by the intravenous injection of potassium salts, the venous pressure remains high even though the arterial pressure is maintained by massage. The venous pressure does not fall until a vigorous heart beat is established, and a rise in the venous pressure will be the signal that the cardiac arrest is recurring.[12] This central circulatory failure with a rising venous pressure has been described in human beings by some as a failure of rapid transfusion to bring about a response in massive hemorrhage.[13] Unquestionably, the measurement of right auricular pressure is of great value. If it is low, it is an indication of hypovolemia. If it is high, it may be a result of overtransfusion,[14] late hemorrhagic shock, potassium intoxication, or cardiac failure. If blood loss is properly monitored, the distinction can be made and the danger of impending cardiac arrest be recognized. The right auricular venous pressure is the most important single determination which can be made during surgery. Careful scrutiny of the electrocardiogram yields far less information than a mere glance at the venous pressure.

During mild hemorrhagic hypotension (up to 110 mm. Hg), only one-third the quantity of potassium is required to produce cardiac arrest (fig. 2). The resistance to potassium cardioplegia can be enhanced by administration of digitalis. Of the drugs administered to the 157 patients, digitalis was given only 14 times while epinephrine was given to more than 50% of the patients and levarterenol (Levophed) bitartrate was administered in an additional 24. The contractility of the myocardium, which is impaired in potassium intoxication, can often be restored with administration of digitalis.[15] Therefore, digitalis is of great value in antagonizing potassium intoxication. When large blood transfusions are anticipated, it is wise to digitalize the patient preoperatively. If large blood loss is encountered in the undigitalized patient, digitalization should be achieved rapidly by the administration of a rapidly acting digitalis preparation such as lanatoside C. Wycoff has found digitalis of value in reducing a rising venous pressure in a patient with massive hemorrhage and blood replacement.

More recently, we have found that glucose and insulin injections favorably effect revival of animals from cardiac arrest induced by the injection of potassium salts during hemorrhagic hypotension. Mavor has commented on the favorable action of glucose in restoring cardiac function in dogs after potassium-induced arrest. Ventricular fibrillation can be consistently produced in dogs if prolonged hypercapnia produced by carbon dioxide inhalation is suddenly alleviated by substituting room air. This type of ventricular fibrillation has been shown to be accompanied by hyperpotassemia. It can be prevented by injections of insulin.[16] If glucose and insulin are protective against potassium-induced cardiac arrest, then epinephrine must exert a noxious effect by inducing further liberation of hepatic potassium. The cardiac effect of epinephrine might soon be offset by its adverse influence on serum potassium. On the other hand, isopropylarterenol (Isuprel) has practically no influence on the liberation of glucose and potassium from the liver. At the same time, the direct cardiac effect of isopropylarterenol is 10 times that of epinephrine. Although recent publications still advocate the use of epinephrine, the Los Angeles County Heart Association has added isopropylarterenol to its regime. Unlike epinephrine, isopropylarterenol does not cause vasoconstriction and is less likely to cause fibrillation. A dose of 0.02 to 0.04 mg. diluted in 10 cc. of saline solution can be injected directly into the left ventricle.

In the past, a number of factors have been alluded to as the cause of cardiac arrest. Anoxia unquestionably is a potent etiological condition, but one questions why the energy mechanisms run out in periods of minutes or seconds during anoxic episodes. This is contrary to our knowledge of muscle contraction, since the energy-yielding substances—adenosine triphosphate (ATP) and phosphocreatine—are already contained in the muscles. Oxygen is required to resynthesize these high-energy phosphates. Perhaps some of the adverse effect of anoxia can be ascribed to the rapid mobilization of liver glucose and potassium. Harris and co-workers studied the excitatory factors responsible for the ventricular fibrillation which followed ligation of the anterior descending coronary artery in the dog: It was the potassium which diffused from the infarcted portion of the myocardium which induced fibrillation in the uninvolved portion. Cherbakoff confirmed and extended this work to show that in those animals in which insulin lowered the potassium concentration of the coronary sinus, no fibrillation developed. Unquestionably, the anoxic effect is really a potassium effect. Stewart has effectively demonstrated that liver anoxia can release sufficient hepatic potassium to induce conduction changes in the heart.[16] The toxicity of hyperpotassemic blood is added to the physiological effects of anoxia.

Hypercapnia has been implicated as an etiological factor in cardiac arrest. The recent work of Nahas showed that dogs rendered apneic by cross-clamping of the trachea after expansion of the lungs with oxygen could survive prolonged periods if tri-hydroxymethyl aminomethane (THAM) were infused intravenously as a buffer. This remarkable buffering substance preserves the pH of the blood and animals show none of the usual toxic signs of hypercapnia. The blood potassium level does not rise and the blood pressure is not elevated from stimulation of the adrenals. It is therefore apparent that carbon dioxide tension is not as important as pH in its influence on homeostasis. Since the lung is not the only organ involved in acid-base balance, impaired renal function in hypovolemic animals can be of great consequence. If the blood is properly buffered with tri-hydroxymethyl aminomethane, the excess carbon dioxide does not induce intense stimulation of the adrenals or a rise in concentration of potassium in the circulating plasma. In the control animals who breathe high concentrations of carbon dioxide or whose tracheas are cross-clamped, the potassium level rises appreciably. It would seem that hypercapnia unmodified with tri-hydroxymethyl aminomethane is an effective means of elevating the extracellular fluid potassium level, and if carbon dioxide is separated from these adverse effects by infusion of tri-hydroxymethyl aminomethane, no change occurs.

It is difficult to accept the fact that a vagovagal reflex can be responsible for more than a few cases of cardiac arrest. This type of cardiac arrest cannot be easily produced in experimental animals. Most patients in the operating room have been preoperatively atropinized. Although some contend that the size of the dose used as a preoperative medicament is ineffective in completely nullifying vagal effects, it certainly is adequate to prevent cardiac arrest induced by intense stimulation of the vagus nerves. In animals and human beings, cardiac arrest does not occur even when the exposed vagus nerve is stimulated by faradic currents. It is doubtful whether any vagal stimulus in clinical cases would be as intense as the stimuli utilized in the attempts to produce cardiac arrest in dogs.

Selective refrigeration of the heart and great vessels also plays a role in transfusion arrest. When cold blood is rapidly administered to the hypovolemic patient, the temperature of the heart is lowered far more than the temperature of the entire body. Since blood once circulated will come into equilibrium with a body mass about 20 times as great as the mass of the blood transfused, blood will be warmed by one circulation through the body. During hemorrhagic hypotension, venous return is so reduced that the rapid transfusion of cold blood may so refrigerate the heart that one may get the sensation of touching a cold metallic object when grasping the heart for massage. We have encountered this in two patients with cardiac arrest when cold blood was administered rapidly. In addition, refrigeration causes potassium to leave the erythrocytes; this potassium enters the cell again after two to three hours of warming.[17] For that reason the plasma-potassium concentration of transfused blood will depend partly on how long the blood has been allowed to equilibrate with room temperature. Normally, sodium diffuses into the red blood cell and a biochemical mechanism pumps the sodium from the cell. Biochemical reactions keep sodium out of the cell and potassium in the cell. During refrigeration, these reactions are slowed sufficiently to allow potassium to diffuse into the plasma. Refrigeration enhances the sensitivity of the myocardium to arrhythmias and contributes to the potassium content of the transfused blood.

Methods for reducing the plasma potassium concentration of stored blood have been investigated. Packets of sodium-saturated cationic-exchange resins are quite effective in keeping the serum potassium values at levels no greater than 5 mEq. per liter even after three weeks of storage. The resin is contained in a small plastic bag which is permeable to alkaline metal ions. The usual citrated anticoagulants can be used, or, if preferable, heparin can also be used. Blood is drawn into the donor bottle in the usual manner and the usual administration set is used. In the absence of the ion-exchange resin bottle, it is imperative that fresh blood be used in all patients in whom massive transfusions appear likely to be needed. Often these needs can be anticipated by special procurement prior to surgery. Unfortunately many cases arise as emergencies, making it impossible to procure any quantity of fresh blood. In some of the cases of cardiac arrest, blood losses were encountered far in excess of the fresh blood available and recourse to bank blood was necessary when the supply of fresh blood was exhausted. While citrate infusion alone does not induce cardiac arrest,[18] it can increase the toxic effect of potassium by temporarily altering the $K^+:Ca^{++}$ ratio.[2] Calcium levels are quickly restored by mobilization of calcium from the bones. When blood is being rapidly transfused during hemorrhagic hypotension, the rate of citrate injection may exceed the rate of endogenous calcium mobilization. For this reason, the injection of calcium salts, either as the gluconate or the chloride, seems advisable. Calcium can be used liberally when blood potassium levels are high so that the the $K^+:Ca^{++}$ ratio is restored. Not the absolute level of calcium but the $K^+:Ca^{++}$ ratio is the factor in initiating ventricular fibrillation. For this reason, calcium administration is safe even when digitalis is used. In 13 of 50 patients with transfusion arrest, calcium was given. It was mentioned as being effective in 4 of the 13 cases. Of all the substances tested, Kay found calcium to be the most effective in his experiments with cardiac arrest. Calcium salts given intravenously during hypercapnia and on ventilation of room air, successfully prevents the induction of posthypercapnia fibrillation in dogs.[16] Calcium antagonizes potassium satisfactorily, but unfortunately therapeutic levels of calcium in the circulating blood can be sustained only momentarily. This is the chief disadvantage of intermittent calcium therapy. Magnesium salts have an effect similar to calcium salts.

Summary and Conclusions

The major cause of cardiac arrest in this series of 157 patients has been potassium intoxication induced by the rapid infusion of large quantities of bank blood. Bank blood contains high concentrations of extracellular potassium, depending on the age of the blood. Endogenous release of potassium from the liver during hemorrhagic hypotension further increases the circulating potassium concentration. An important factor is the proper monitoring of blood loss so that hypovolemia, even though fully compensated, does not develop during surgery.

Fresh blood, or blood treated with ion-exchange resin, has a low potassium concentration and is relatively safe. Rapid transfusion of ice-cold blood selectively refrigerates the heart. Digitalis antagonizes potassium intoxication both preoperatively and peroperatively. A rise in venous pressure during operation may indicate a failure of cardiac contractility secondary to an elevated blood potassium concentration. Peripheral venipuncture may fail to disclose elevated potassium values during potassium intoxication. The potassium concentration of blood obtained by cardiac puncture may be considerably elevated. Isopropylarterenol (Isuprel) rather than epinephrine should be used as a cardiac stimulant.

Drs. Clarence Dennis, Merel Harmel, Philip Cooper, and William McFee permitted use of the clinical material at Kings County Hospital, Bronx, and Manhattan Veterans Administration Hospitals.

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J.A.M.A., June 18, 1960

MASSIVE HORMONAL THERAPY AND SPLENECTOMY IN ACUTE THROMBOTIC THROMBOCYTOPENIC PURPURA

REPORT OF THREE CASES WITH ONE EIGHT-YEAR CURE

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and
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Apparent recovery in two out of three cases of thrombotic thrombocytopenic purpura was attributed to massive treatment with corticotropin and prednisolone. The role of splenectomy, performed in each case, was not so clear. The death of one patient, treated only with ACTH, was associated with extensive adrenal involvement. The essential clinical and laboratory findings characteristic of this disease were illustrated in these cases. The urgency of early diagnosis was stressed because the usual, rapid deterioration of the condition of a patient with acute thrombotic thrombocytopenic purpura apparently was prevented by the intensive hormonal therapy described.

Three cases of fulminating thrombotic thrombocytopenic purpura are reported below, because of an eight-year cure of one patient and a two-year survival, without relapse, of another. In a third case, failure of therapy and death may have been related to an unusual degree of involvement of the adrenals, as demonstrated at autopsy.

The clinical syndrome of bizarre neurological manifestations, severe thrombocytopenia, hemolytic anemia, and fever was first described by Moschcowitz[1] in 1925. The essential lesion was considered to be due to platelet thrombi of small vessels.

The term "thrombotic thrombocytopenic purpura" was first applied to this condition by Singer and co-workers[2] in 1947. They considered the disease to be a hemorrhagic disorder, with generalized platelet thrombosis. Since that time, many different suggestions have been offered to explain the unusual features of this disease: for example, endothelial injury attracting deposition of platelets,[3] collection of subendothelial hyaline material,[4] hyperergic damage to vessel walls by antigens,[5] the Shwartzman phenomenon,[6] and endothelial antibodies.[7] It has generally been agreed that the maximum damage occurred at the arteriole-capillary junction. Although the actual etiology of the syndrome is unknown, Talbott[8] suggested that it may be related to collagen disease because of (1) the specific lesion's having the same staining characteristics as collagen and (2) the postulated etiological mechanism of hypersensitivity.

The literature has been reviewed extensively by Antes[9] and Wasserman,[10] who reported some 63 cases up to June, 1956. The disease is still considered to be uniformly fatal by most authors.[11] However, at the time of writing, at least five patients are known to be in remission.[12] The longest remission at the time of reporting, with the patient apparently still living, was 38 months.[13] The diagnosis, however, was clinical and not based on biopsy in this case. The patient in the case of Siegel and associates,[12d] confirmed by biopsy, had been in remission for 32 months and was still living at the time of their report.

Report of Cases

CASE 1.—A man, aged 49 years, was first seen at Baylor Hospital in August, 1951, in a semicomatose state. His illness dated back to three weeks prior to admittance and manifested itself by severe headache, dizziness, transiently slurred speech, and fleeting episodes of paralysis of the right leg and the right arm; several days later a similar episode involved the left side of his body. On the day of admission he was semicomatose. His medical history revealed his having had pulmonary tuberculosis, arrested seven years after performance of pneumothorax, and tonsillectomy which had been performed six months prior to admission.

The patient was a well-developed, well-nourished man, who appeared semicomatose and incontinent, responding only to painful stimuli. His temperature was 100.4 F (38.0 C), pulse rate 100 per minute, respiration rate 25 per minute, and blood pressure 122/78 mm. Hg. The skin was icteric; the heart and lungs were normal; and the abdomen was soft, without palpable masses. At fundoscopic examination, the right optic disk was normal but for several flame-shaped hemorrhages along the lower disk margin; the left disk could not be visualized. The lower part of the right side of his face was paralyzed, and there was a constant, restless motion of the left arm, while the right arm was completely flaccid. The deep tendon reflexes were absent on the right but hyperactive on the left side, while the patellar and ankle reflexes were hyperactive bilaterally.

The patient became unconscious shortly after admission. The laboratory findings revealed a hemoglobin level of 6.7 Gm. per 100 cc., a reticulo-

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From the J. K. and Susie L. Wadley Research Institute and Blood Bank, and the Department of Pathology, University of Texas Southwestern Medical School.

cyte count of 37%, and 13,900 platelets per cubic millimeter. Because of the typical clinical and laboratory findings, the diagnosis of fulminating thrombotic thrombocytopenic purpura was postulated, and the patient was immediately treated with blood transfusions (three in number) and intravenously given ACTH (fig. 1). The next morning, there was marked improvement, and the patient had regained consciousness. ACTH therapy was continued by both intravenous and intramuscular route daily, with clinical improvement. In the nine days prior to splenectomy, a total of 205 mg. intravenously and 245 mg. intramuscularly was administered, with a maximum dose in one day of 40 mg. by the intravenous and 50 mg. by the intramuscular route. The number of platelets increased to 94,000 per cubic millimeter and the hemoglobin level rose to 13.4 Gm. per 100 cc.; a splenectomy was performed at that time (10 days after admission).

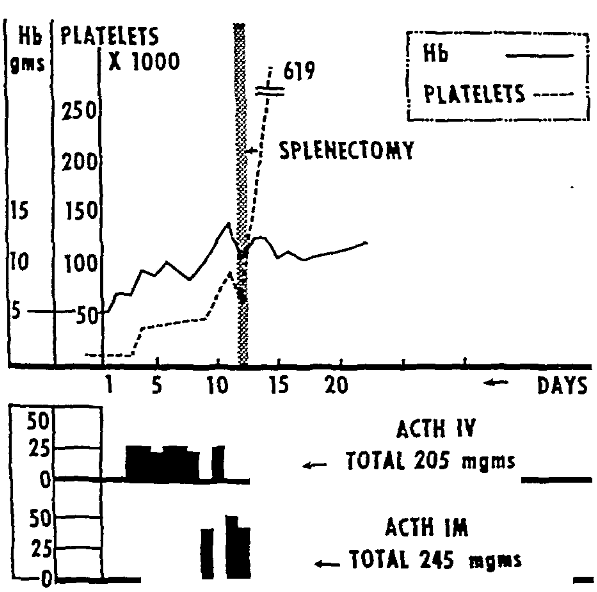

Fig. 1 (case 1).—Thrombotic thrombocytopenic purpura: illustration of course, with use of massive doses of ACTH and splenectomy.

After operation, the platelet count rose to 400,000 per cubic millimeter within four days. No further transfusions were required; the reticulocyte count and icterus index dropped to normal levels. The patient's postoperative course was uneventful, with continuous improvement of his neurological manifestation. He was discharged 22 days after admission.

Pathologically, the spleen showed chronic passive hyperemia, reticuloendothelial hyperplasia, and fibrinoid thrombi of small arteries characteristic of thrombotic thrombocytopenic purpura (fig. 2). No inflammatory infiltrates were seen in the involved small arteries. A few myelocytes, rare normoblasts, and a few megakaryocytes were noted in the splenic pulp.

This patient has been seen in follow-up at regular intervals and continues to feel well while engaging in normal activities. Results of physical examination in November, 1957, were normal, as were the hemoglobin level at 15.4 Gm. per 100 cc. and the platelet count at 543,000 per cubic millimeter. To date, as of February, 1960, the patient continues to be well.

Case 2.—A 29-year-old man was admitted to Baylor Hospital in June, 1954, with the chief complaints of frontal headache, vomiting, purpuric rash on his lower extremities, and dark brown urine for five days. His medical history appeared noncontributory.

On physical examination, the patient appeared to be an acutely ill, somewhat lethargic man who answered questions slowly. The only other positive finding was that of a liver palpable 3 cm. below the right costal margin.

On admission, laboratory findings included 8,500 white blood cells per cubic millimeter, with a differential count of 1% eosinophils, 11% band cells, 74% segmented cells, 12% lymphocytes, and 2% monocytes; hemoglobin level 8.8 Gm. per 100 cc.; and 2,830,000 red blood cells per cubic millimeter. The patient required nine blood transfusions for anemia during his hospital course. His first platelet count was 23,360 per cubic millimeter and remained near 30,000 until the day after operation, when it increased to 108,000.

Urinalysis on admission revealed a specific gravity of 1.020, acid reaction, 500 mg. % concentration of albumin, no sugar, and occasional white and numerous red blood cells. A few days later, the serum bilirubin concentration ranged from 0.2 to 0.7 mg. % for direct and from 1.9 to 2.4 mg. % for indirect reaction; the blood urea nitrogen level was 30.5 mg. %. The bone marrow showed normal fulness, with increased activity of nucleated red blood cells; megakaryocytes were normal. The prothrombin time was 58% of normal, and prothrombin utilization was 50%; the time for proconvertin was 45% of normal and for proaccelerin 100% of normal. Result of Coombs' test was negative, and erythrocyte fragility was normal on one occasion and decreased on another.

Although it was first thought that this patient might have acute nephritis, septicemia with purpura and acute hemolytic anemia were also considered. Two days after admission, the patient complained of restlessness and weakness, accompanied by poor appetite and lethargy. There being the possibility of hemolytic anemia, ACTH therapy was initiated on the third day, and a total of 280 mg. intramuscularly and 60 mg. intravenously was given over a six-day period. Five days after admission the patient became more confused. Neurological examination revealed no retinal hemorrhages; disk margins were somewhat blurred, and nuchal rigidity was present. At this time, a diagnosis of thrombotic thrombocytopenic purpura was made, in view of the anemia and reticulocytosis, hemolytic anemia, and mental confusion. Splenectomy was advised and performed seven days after admission. The patient withstood the procedure well but developed hemiplegia on the right side and the next day suffered a convulsion. He died 10 days after admission.

The autopsy findings were those of fibrinoid material found occluding, or partially occluding, arterioles and capillaries in most of the organs including brain, kidney, testes, heart, spleen, lymph nodes, and bone marrow. Few lesions were found in the thyroid, liver, and lung. The hyaline thrombi were especially prominent in capillaries and sinusoids of the adrenal cortex, with areas of hemorrhage and early necrosis and lipid depletion (fig. 3). Results of histochemical studies of fibrinoid thrombi were not conclusive. The lesions, however, were considered typical of thrombotic thrombocytopenic purpura.

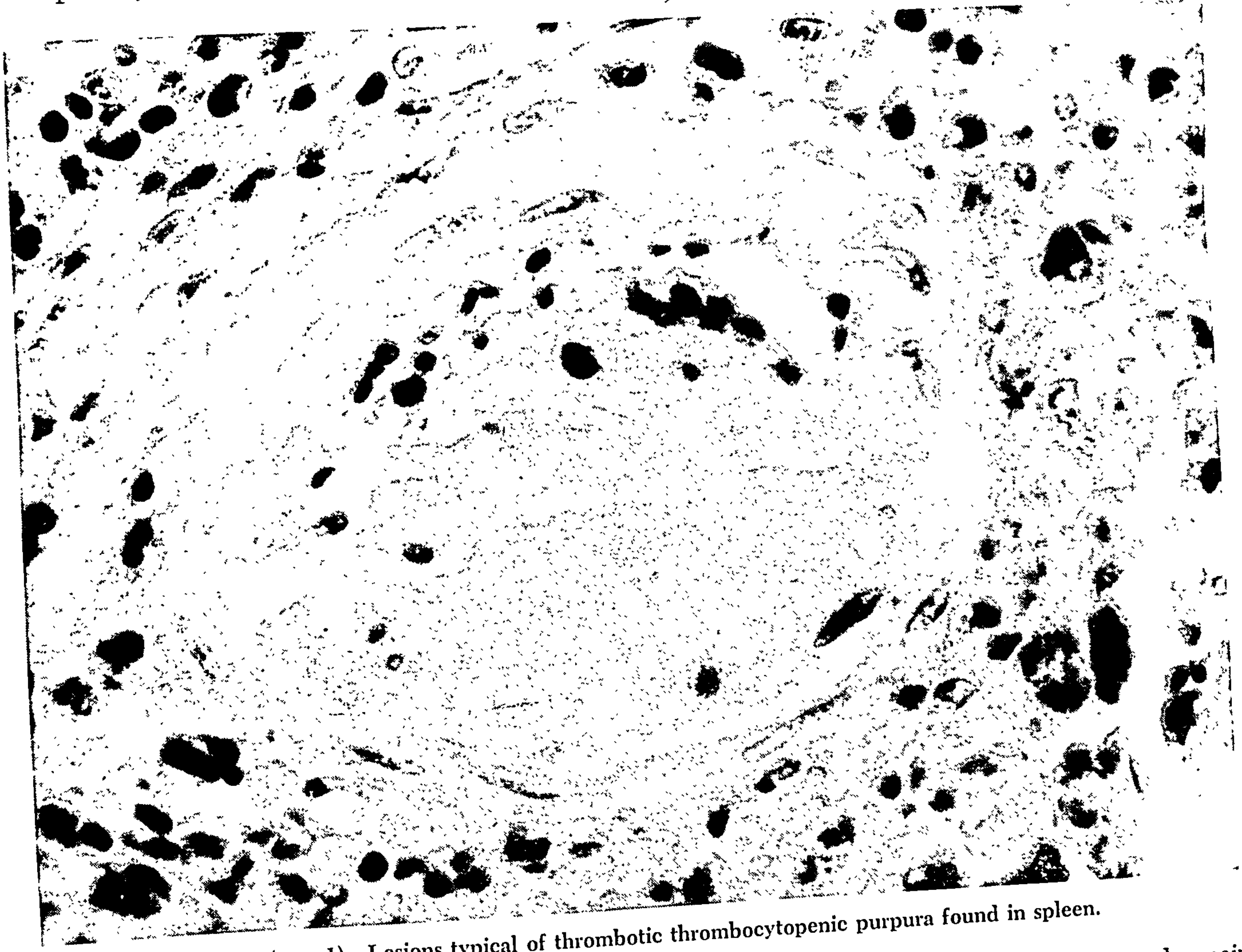

Fig. 2 (case 1).—Lesions typical of thrombotic thrombocytopenic purpura found in spleen.

Case 3.—A 33-year-old woman was admitted to Baylor Hospital on Nov. 13, 1957, complaining of numbness, tingling, and pain in the left hand of 10 hours' duration, followed by episodes of cyanosis of the left hand and forearm. The patient had recently received poliomyelitis vaccine; her medical history was otherwise not remarkable.

The physical examination on admission was remarkable only because of the severe pain in the left hand, with absence of the radial and ulnar pulses in the left forearm. The brachial pulse in the left arm was present, and all other peripheral pulses were present and equal. The impression gained from examination was that of occlusion of the left brachial artery at the level of the bifurcation into the radial and the ulnar artery, of unknown etiology, but with consideration that emboli might be present.

Laboratory findings on admission showed the leukocyte count to be 8,600 per cubic millimeter, with a differential count of 87% segmented cells, 12% lymphocytes, and 1% monocytes, and remaine normal all during the hospital course. The hem globin level was 13.6 Gm. per 100 cc. On the eighth day after admission, the hemoglobin content dropped to its lowest level, 8.5 Gm. per 100 cc., with 3,200,000 erythrocytes and a platelet count of only 20,000 per cubic millimeter. The patient was then given blood transfusions (a total of 2,000 cc. in two days). There was a steady rise in the platelet count while the patient was receiving large doses of prednisolone and ACTH, but there was a decided drop once the steroid dosage was decreased. On the 34th day (the day prior to splenectomy), the hemoglobin level was 9.9 Gm. per 100 cc. and the platelet count 110,000 per cubic millimeter. After operation, the hemoglobin, erythrocyte and platelet counts returned to normal, and the patient's last peripheral count before discharge was 12.4 Gm. per 100 cc. of hemoglobin, 4,100,000 red blood cells per cubic millimeter, and 781,000 platelets per cubic millimeter. The serum bilirubin level was 0.0 mg. % direct and 1.68 mg. % indirect. The spinal fluid was normal, and the results of both the Coombs' test and the L. E. test were negative.

During the first four weeks of the patient's illness, her temperature ranged from 100 to 102 F (37.8 to 38.9 C) and then returned to normal. On admission embolectomy was performed, but the symptoms persisted. A stellate ganglion block was given when another clot was removed from the brachial artery, at which time she was given heparin sodium.

On the eighth day, there was definite improvement in the occlusion of the brachial artery in the patient's left arm, and another clot was removed; on the next day, however, the patient developed significant changes manifested by hemiplegia on the left side. At this time, hematological consultation was requested, and the diagnosis of thrombotic thrombocytopenic purpura was suggested because of the thrombocytopenia, hemolytic anemia, neurological changes, and fever. This was thought to be an unusual case because of the occlusion of the large artery. A neurosurgeon who was consulted suggested that the central nervous system manifestations were due to an extension of an occlusive disease of arterial blood supply to the right hemisphere. The cerebral lesion progressed during the succeeding days, causing a generalized spasticity of both extremities. The pupils were equal, and the eyes wandered to the left in conjugate movement; bilateral lesions were suspected. With the fulminating progression of the disease, the decision was made to treat it as a thrombotic thrombocytopenic purpura with massive doses of prednisolone and ACTH, followed by splenectomy.

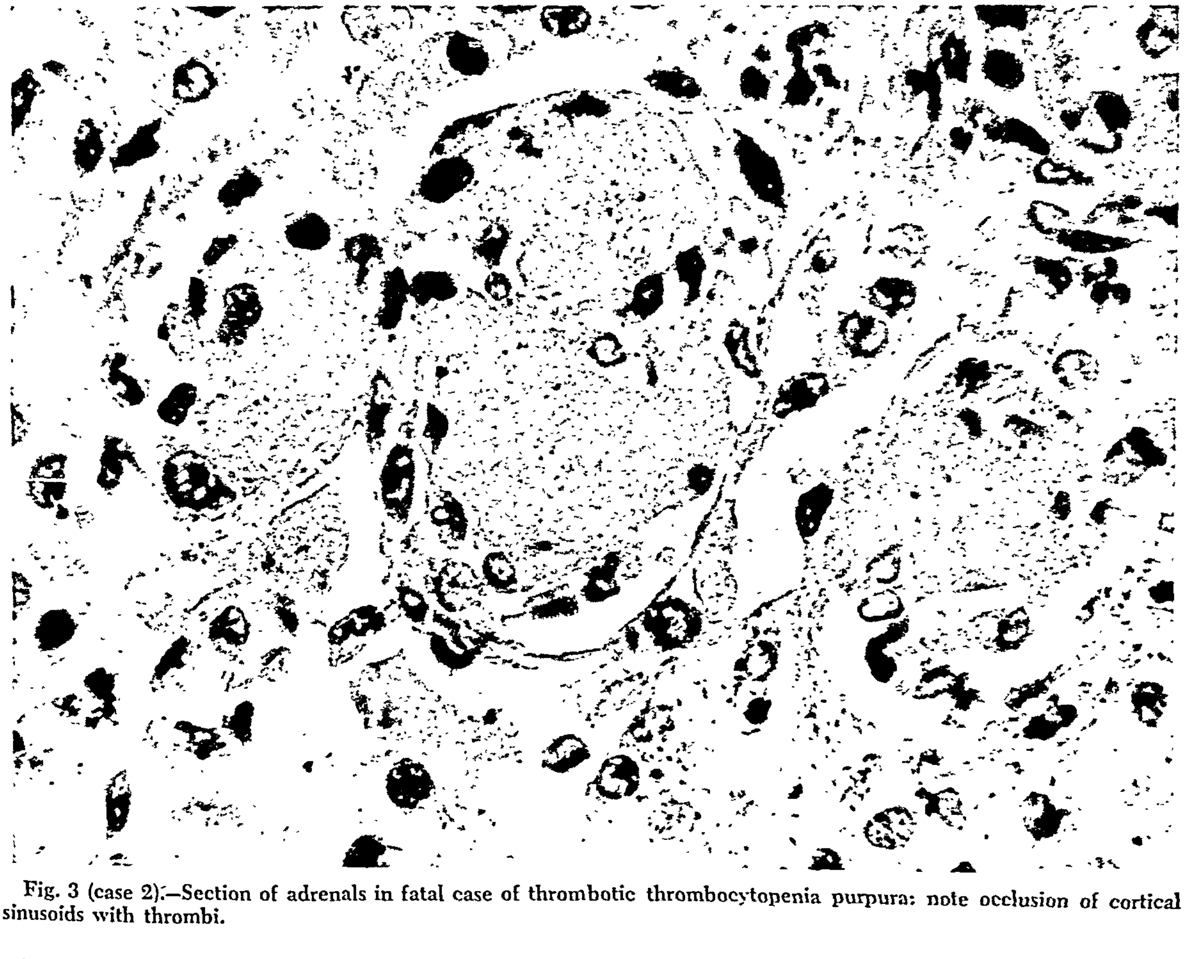

Fig. 3 (case 2).—Section of adrenals in fatal case of thrombotic thrombocytopenia purpura: note occlusion of cortical sinusoids with thrombi.

The patient's clinical course is shown in figure 4. The patient was given a total of 1,400 mg. of ACTH intravenously, 1,130 mg. of ACTH intramuscularly, 1,150 mg. of prednisolone intravenously, and 335 mg. of prednisolone orally over a period of 30 days.

During the massive steroid therapy, the patient developed no further thrombi but continued to be confused and stuporous; on decreasing the steroid dosage, however, a definite drop in the number of platelets was observed. Splenectomy was suggested, with the idea that steroid therapy should be completely discontinued after splenectomy to meet the eventuality that the steroids might have been playing a role in the patient's mental condition. Splenectomy was performed five weeks after onset of the illness. After the operation the patient had an uneventful recovery. Her peripheral blood count returned to a normal level, and there was a slow but progressive clearing of her mental confusion. The patient was discharged with only residual spasticity of her legs and right hand.

Pathological diagnosis of the amputated left arm and the spleen was that of thrombosis of the left radial artery, gangrene in the left hand, and late vascular lesions of the spleen, compatible with a late stage of thrombotic thrombocytopenic purpura.

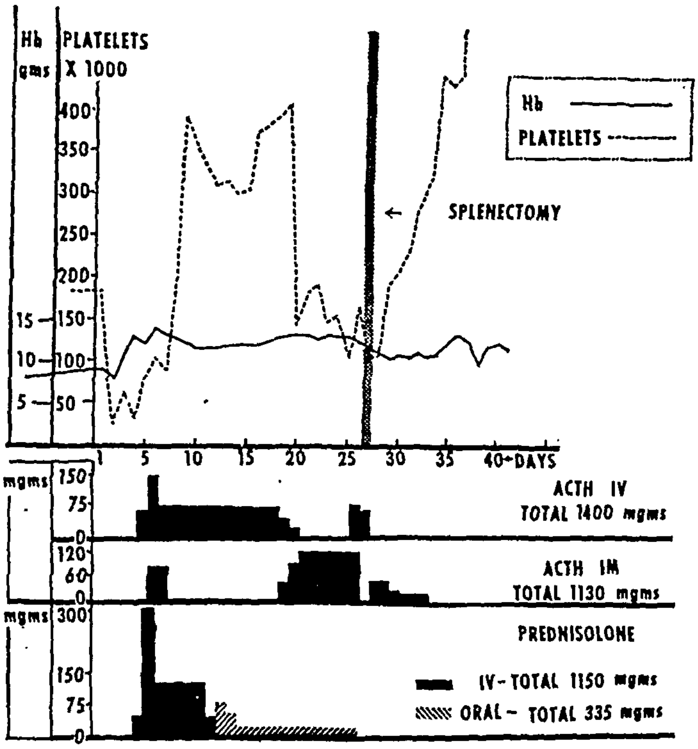

Fig. 4 (case 3).—Thrombotic thrombocytopenic purpura: relationship of therapy with massive doses of ACTH, steroids, and splenectomy to clinical course.

Follow-up of this patient's progress in February, 1960, indicated a continuing hematological remission of her disease. The latest platelet count (August, 1958) was 298,000 per cubic millimeter.

Comment

The generally accepted concept of thrombotic thrombocytopenic purpura as an inevitably fatal disease may now be questioned. Sufficiently massive therapy with ACTH, steroids, or both, may be highly effective in arresting this disease, as illustrated in two of the three cases reported. The role of splenectomy cannot be clearly assessed. The successful result in the first case prompted the use of this procedure in the other two. It was of interest to note that most of the patients with reported cases of thrombotic thrombocytopenic purpura who survived one year or more had splenectomy performed. Burke and Hartmann,[14] however, reported the cases of two patients with apparently less severe forms of the disease, who had remissions of 38 months and 20 months, respectively, and suggested that steroid therapy might prevent development of the fulminating phase of the disease.

Since all three cases in this report were of the acute fulminating type, the good results in two of these may reasonably be attributed to the therapy rather than to spontaneous remission. In the first case, the patient's survival for over eight and one-half years, with continuing good health and no sign of relapse, seems to justify the designation "eight-year cure." The second case must be considered a complete therapeutic failure, possibly due to the inability of the severely involved renal cortex to respond to ACTH injections. The patient in the third case, despite the somewhat delayed treatment, showed a prompt response to administration of massive doses of prednisolone and corticotropin, with no sign of relapse two years after splenectomy.

From so few cases, generalization cannot be made that all patients with thrombotic thrombocytopenic purpura will respond to steroids given in sufficiently large doses. Other reports, however, citing reasonably long remissions, describe the use of fairly large doses of ACTH and cortisone, the former in intravenous doses of up to 75 mg. per day and the latter in doses of up to 300 mg. daily. Periods of survival of 13 to 32 months after similar treatment have been reported, with each of the three patients living at the time of the reports. Of 22 additional patients reported in the same interval, all died; only 2 of these received steroids in small doses and had splenectomy performed. The remaining patients either received small doses of steroids only, had splenectomy without steroids, or received neither. Worthy of mention is the recent report of Bernstock and Hirson[13] of a remission of thrombotic thrombocytopenic purpura on treatment with heparin, although prednisolone and corticotropin also were used.

Rapid therapeutic response appears vital because of the acute fulminating nature of most of the reported cases of thrombotic thrombocytopenic purpura. Success in treatment, it seems, would require early recognition, followed by massive hormonal therapy, prednisolone or prednisone in doses of 1 Gm. daily by mouth or 100 to 200 mg. by vein being recommended. Concomitant intravenous administration of corticotropin and subsequent splenectomy may not be essential, but one should hesitate to omit these procedures in so grave an emergency.

Massive hormonal therapy may be necessary to break up the autoimmune hypergic mechanism or other unknown processes responsible for the acute manifestations of this disease. Favorable responses to massive steroid therapy have been observed, for example, when conventional doses have failed in cases of acquired hemolytic anemia and thrombocytopenia. One should not hesitate to use these massive doses in acute emergencies such as this disease presents, since extensive experience with massive, short-term steroid therapy in patients with leukemia and other blood dyscrasias has not shown an appreciable increase in side-effects.[15]

Diagnosis should be confirmed by biopsy, and for this purpose bits of bone marrow, endometrial scrapings, lymph nodes, spleen, and other tissue sources have been used successfully. Clinical recognition, however, should not be difficult if the following four characteristics are established: (1) hemolytic anemia, (2) thrombocytopenia, (3) central nervous system symptoms, and (4) fever.

The pathogenesis of thrombotic thrombocytopenia is less understood than its characteristic pathology. The usually negative result of the direct Coombs test for sensitized erythrocytes, and the observation of Brittingham and Chaplin [16] that no measurable changes or reaction occurred in a normal volunteer on infusion of 300 ml. of plasma from a patient with a fatal case do not suggest a direct antibody mechanism. However, the favorable and immediate response to steroid therapy and prolonged remission are not inconsistent with the concept of collagen disease.[8]

Summary

Two of three patients with acute thrombotic thrombocytopenic purpura showed a dramatic response to massive therapy with ACTH, steroids, or both, followed by splenectomy. Survival for over eight years of one patient and two years of another, without relapse, suggests revision of the concept of uniform fatality. The death of one patient treated with ACTH may be related to extensive adrenal damage. One of the patients responding to therapy presented certain atypical features, including thrombosis of large vessels.

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The ACTH used in this study was supplied by the Armour Pharmaceutical Company, Kankakee, Ill., as ACTHAR, and the prednisolone by the Schering Corporation as Meticortelone.

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CLINICAL NOTES

CONGESTIVE FAILURE DUE TO AURICULAR FIBRILLATION IN AN OTHERWISE NORMAL HEART

REPORT OF A CASE WITH TWENTY-FIVE YEAR FOLLOW-UP

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and
John R. Flanery, M.D., *Portland, Ore.*

The fact that auricular fibrillation may occur in a patient with an otherwise normal heart is generally accepted. However, that severe congestive failure may develop under such circumstances is not so well known. Since this type of heart disease is completely reversible, the importance of its recognition is apparent. Although a number of such cases h been recorded in the literature,[1] it appears prob that many other cases remain unrecognized; t some patients are denied a chance for recover

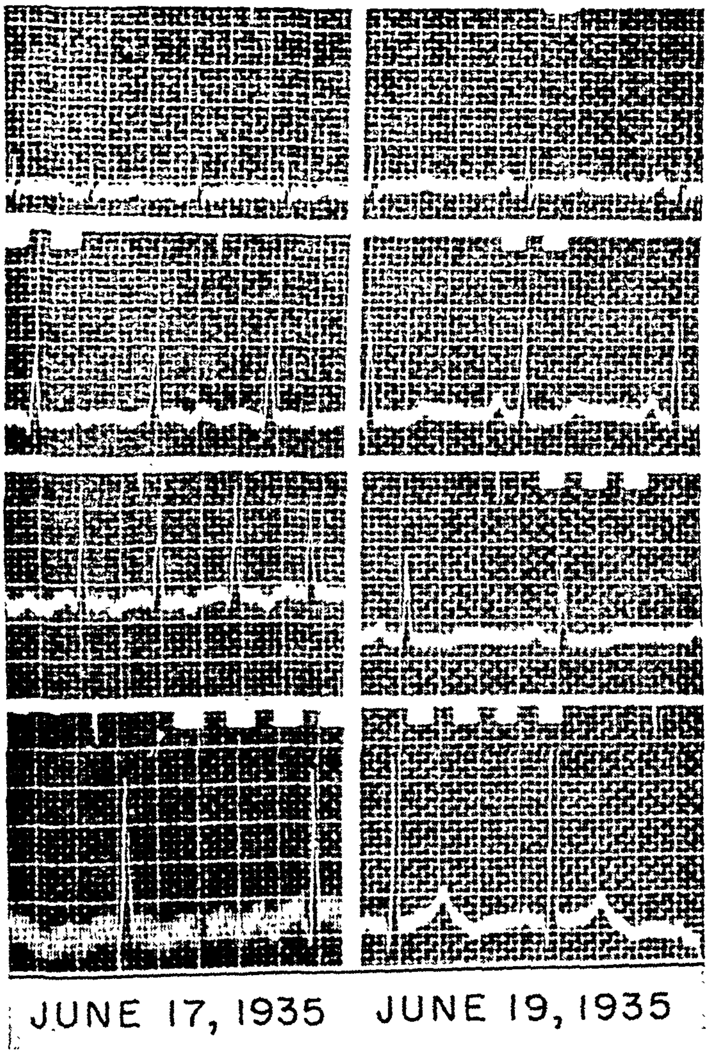

Fig. 1.—*Left,* ECG (3 standard limb leads and chest lead CF4) taken June 17, 1935, on ninth day of digitalization. Auricular fibrillation is still present; average ventricular rate is still over 100 per minute. *Right,* ECG taken after quinidine therapy, two days later. Note normal sinus rhythm present, with average ventricular rate of about 76 per minute.

A 25-year follow-up is presented of a case pr ously reported in 1937 [1a] and in 1947.[1b] The pati a woman, was first seen in June, 1935, at 43 y of age. She was in severe congestive failure a having had uncontrolled auricular fibrillation three months. Compensation was established means of digitalis, diuretics, and diet, and nor sinus rhythm was restored with quinidine thera (fig. 1). Rapid recovery followed. All medicati was discontinued, and, within one month, the p tient resumed her normal life, which included a tive, even strenuous social and business duti During the following 25 years, she continued excellent health; repeated physical and laborat examinations have always yielded normal findin

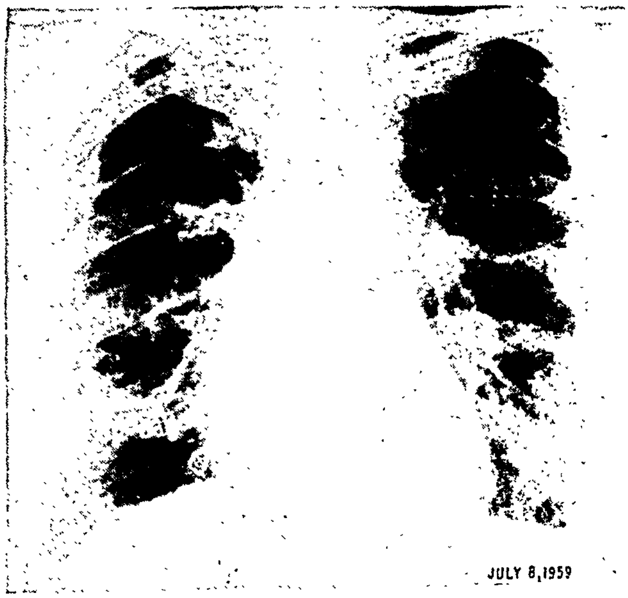

Fig. 2.—Roentgenogram taken July 8, 1959. Heart rem normal in size, shape, and position. Calcification of ao knob is now present; lung fields remain clear.

As indicated in the original report of 1937 there was nothing in the patient's history or exan

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nation to suggest any known type of heart disease, nor has any evidence developed in the ensuing 25 years to suggest it. At 68 years of age her blood pressure remains normal and her heart is normal on physical, roentgenographic and electrocardiographic examinations (fig. 2, 3).

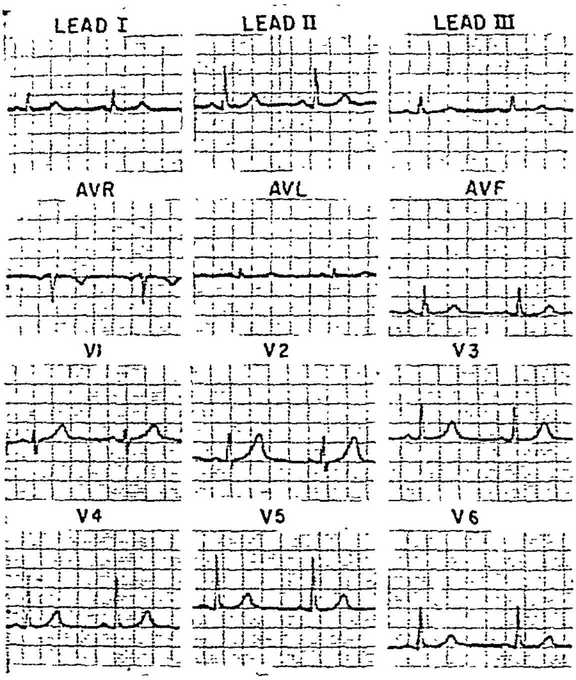

Fig. 3.—ECG taken July 8, 1959; normal tracing.

This case is unique because of the unusually long follow-up. The fact that the heart has remained clinically normal, measured by the strictest standards, over 25 years of active life would appear to offer convincing proof of the absence of significant myocardial disease. Thus, this case may be accepted as sound evidence that (1) auricular fibrillation per se may produce severe congestive heart failure in an otherwise normal heart, and (2) this type of heart disease may be completely and permanently reversed by establishment and maintenance of normal sinus rhythm after compensation has been restored.

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LONG-TERM SURVIVAL AFTER DISSECTING ANEURYSM OF AORTA

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Edward S. Orgain, M.D., Durham, N. C.

Long survivals after the diagnosis of dissecting aneurysm are rare. The course of a patient suffering from dissecting aneurysm was followed by one of us (E.S.O.) for 16 of the 19 years she lived after this diagnosis was made. A review of the literature indicates that this may be the longest survival of a patient in whom a clear-cut antemortem diagnosis was made at the time of the dissection.

Report of a Case

A 59-year-old married woman was first seen at Duke Hospital in 1941. Her medical history revealed that she had always been susceptible to infection. Besides the usual childhood diseases, she had had pneumonia, scarlet fever, typhoid fever, and puerperal sepsis. In 1929, hypertension was first noted, with the systolic pressure at about 260 mm.Hg. In 1933, she underwent a hysterectomy and right oophorectomy for chronic pelvic inflammatory disease. A preoperative examination had reported the heart to be normal. The blood pressure at that time was 180/90 mm.Hg, and serologic findings were normal. No roentgenogram of the heart was taken.

She remained fairly well until January, 1938, when, while standing before a mirror one afternoon, she was seized by a severe crushing precordial pain that radiated straight through to the back but not into the arms or neck. She was short of breath, became nauseated, and was taken immediately to the hospital. On admission her blood pressure was recorded as 180/90 mm.Hg. The pulse and respiration rates were normal. The heart was described as being enlarged to the left. There was a grade 2 systolic murmur at the apex and a grade 3 systolic murmur at the pulmonic area which radiated to the left clavicle, the suprecalvicular notch,

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and down the left paravertebral area; the mitral first sound was greater than the mitral second sound, and the aortic second sound greater than the pulmonic. The rhythm was normal; no friction sounds were heard.

Results of routine laboratory studies, including blood and spinal fluid tests for syphilis, were negative. Films of the chest were reported as showing marked dilatation of the arch and of the descending portion of the aorta. Findings of gastrointestinal series, barium enema, gallbladder studies, and an abdominal flat plate were reported to be normal. Four electrocardiograms showed no abnormalities. Her severe chest pain persisted, with only partial relief from treatment with heavy doses of morphine. A diagnosis of dissecting aortic aneurysm was made, and the patient remained in the hospital for three weeks.

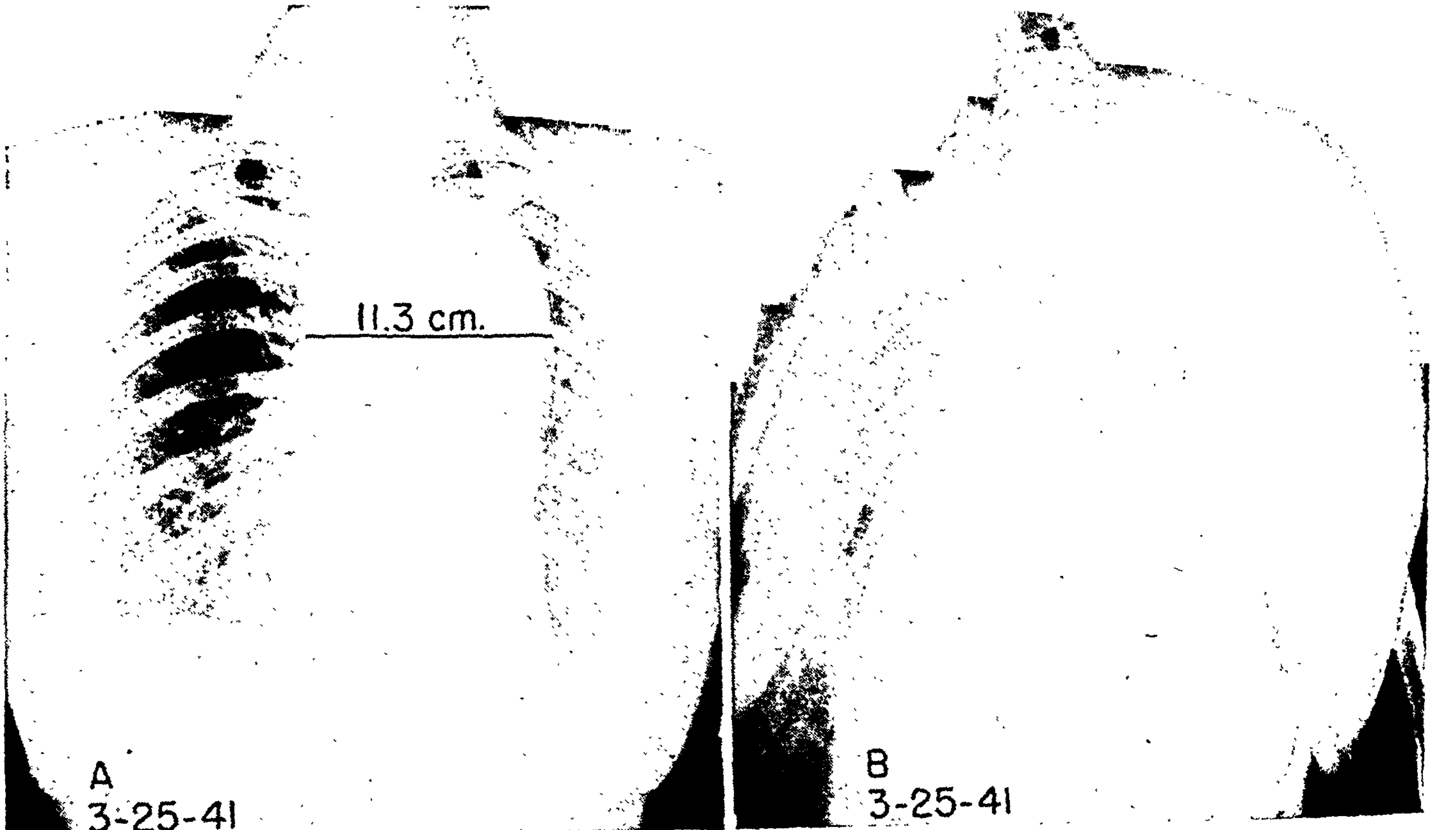

Fig. 1.—Roentgenograms of chest taken three years after dissection of aneurysm. *A*, posteroanterior view: great vessels measure 11.3 cm. *B*, left anterior oblique view, showing aneurysm to involve arch and descending portion of aorta.

For the next year the patient remained in bed. After the initial episode, she continued to complain of a dull aching pain over the precordium which occasionally became severe and was only slightly alleviated by rest. Because of severe shortness of breath and wheezy respirations, she was able to walk only on level ground. Her systolic blood pressure remained in the range of 140 to 160 mm.Hg.

When the patient was first seen at Duke Hospial in 1941, she was well-developed and well-nourished and appeared well. Her fundi showed slight silvering, definite tortuosity, minimal A-V compression, but no hemorrhages or exudates. The trachea was in the midline without tug. There was an obvious systolic pulsation in the jugular notch and in both supraclavicular fossae. The chest was symmetrical. The lungs were normal except for diffuse wheezing respirations, particularly over the left lung. The apical impulse was in the 5th intercostal space, 2 cm. to the left at the midclavicular line. At the apex there was a midsystolic murmur. There was a fairly loud systolic murmur at the pulmonic area and a faint one at the aortic area. The murmurs were transmitted to the left clavicle, the supraclavicular notch, and down the left paravertebral area to the angle of the scapula. Blood pressures were 140/90 mm.Hg in the right arm, 150/92 mm.Hg in the left arm, and 120/100 mm.Hg in the left leg. Peripheral vessels were all felt, but the abdominal aorta and the femoral and popliteal arteries showed weak pulsations. The remainder of the physical examination was not remarkable.

Results of routine laboratory studies, including Kahn and Wassermann tests, were negative. Electrocardiographic findings were normal. Roentgenographic examination (fig. 1) showed an aneurysm of the distal portion of the arch and of the descending portion of the aorta. The supracardiac shadow measured 11.3 cm. These findings confirmed the diagnosis of dissecting aneurysm of the aorta.

Between 1941 and 1953, the patient was seen four times in the outpatient clinic. During that time, she presented a more or less constant, dull aching precordial pain, which sometimes radiated through to the back and occasionally into the left arm. Increasing difficulty with shortness of breath, wheezing respirations, and cough were noted. Her respiratory symptoms were accentuated by lying on her left side. There was no history of cardiac decompensation. Her physical findings had changed somewhat during this interval. A tracheal tug to the left had developed. The right carotid pulse was greater than the left. Dulness to percussion over the left side of the chest both posteriorly and anteriorly was evident. Her blood pressure, however, remained rather stable.

In January, 1957, after a four-year absence from follow-up observation, the patient was admitted to Duke Hospital with abdominal complaints. Two years prior to admission, she had had episodes of abdominal pain, swelling, and diarrhea, lasting for several months. One year later diarrhea recurred. Since that time she had had pain in the abdomen and in the flanks which extended up to the shoulders. This pain was increased by motion, especially bending, and decreased by lying down, belching, or passing flatus. For two months prior to coming to the hospital the patient also had had daily pain in the left lower part of the chest, the left upper quadrant, and the left flank.

Her physical findings had changed only slightly. A systolic thrill was now evident over the base of the heart and also in the left upper side of the chest. There was abdominal tenderness to deep palpation, especially in the left upper quadrant, but no masses were felt. Routine laboratory findings were again normal. A complete roentgenographic survey of the gastrointestinal tract likewise resulted in essentially normal findings. A teleoroentgenogram of the chest disclosed an increase in the size of the supracardiac shadow (fig. 2*A*). She was discharged in somewhat improved condition six days after admission.

The patient's progress was followed at monthly intervals through June 6, 1957, with practically the same complaints as before. An abdominal flat plate taken during that time showed a curved linear shadow at the level of and just lateral to, the left of the first lumbar vertebra (fig. 2*B*). Lateral films placed it posteriorly, and it was thought to represent calcification in the walls of an aneurysm which had extended below the diaphragm.

On June 29, 1959, while witnessing a boating accident, the patient experienced a severe pain in the left side of the chest and became weak and faint. Three hours later, when she was seen by her family physician, she still complained of the chest pain which had become somewhat pleuritic. Her blood pressure was 140/90 mm.Hg. A basal diastolic murmur had became apparent.

Despite sedation, the pain continued. Seven days later, the patient expectorated about 10 cu. cm. of bright red blood. She was taken to her local hospital. On admission, her blood pressure was 200/100 mm.Hg. The left side of her chest was dull to percussion, and breath sounds were absent. A chest x-ray showed that the aneurysm now occupied the upper part of the chest, a fluid level being present

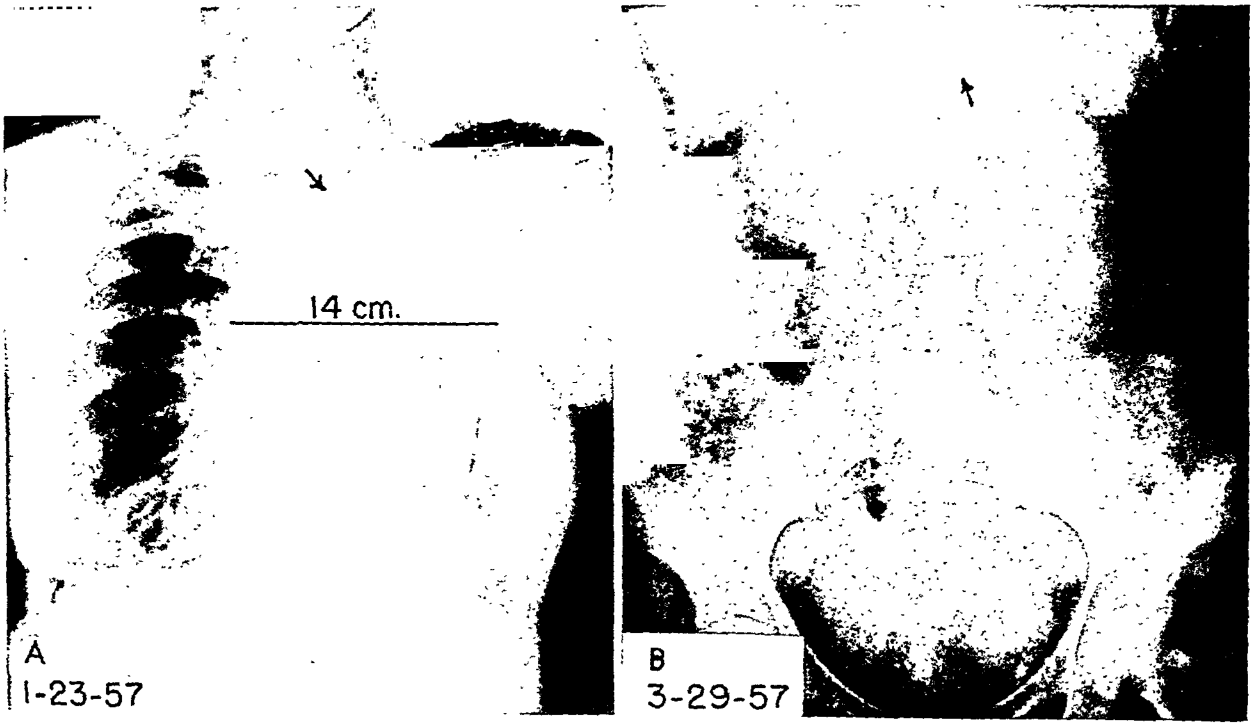

Fig. 2.—Roentgenograms taken 19 years after dissection. *A*, posteroanterior view of chest: supracardiac shadow has increased from 11.3 to 14.0 cm.; *arrow* designates rim of calcium in aneurysm. *B*, abdominal film also shows calcification in wall of aneurysm which had extended below diaphragm.

below (fig. 3*A*). The pain continued, and on July 12 her hemoglobin level was 8.7 Gm.%. A roentgenogram taken on July 13 showed that the entire left side of the chest was filled with fluid (fig. 3*B*). On July 14, 1959, she awoke from her sleep, complained of shortness of breath, became cyanotic, and died immediately. Permission for autopsy could not be obtained.

Comment

It is indeed rare for a person to survive long after developing a dissecting aneurysm of the aorta. Hirst and associates,[1] in their series of 425 collected cases, reported a 99% mortality after five years, the longest survival totaling nine years. Patients with the longest survival time had no clear-cut antemortem diagnosis, and the date of the initial dissection was determined only in retrospect. On this basis, Graham [2] reported a 30-year survival, Bostroem [3] a 22-year survival, and Hall [4] a 15-year survival. Flaxman [5] dated the survival times of 12 patients with silent dissecting aneurysms from the onset of cardiac decompensation and reported only one 12-year survival. In 1946, Jones and Langley [6] observed a patient still alive eight years after a correct diagnosis. The patient died six years thereafter, and autopsy revealed a dissecting aneurysm unruptured at the time of death.[7]

The patient reported by us lived for 19 years after dissection of the aorta. Although autopsy was not performed, the case history and roentgenographic findings are so classic as to leave no doubt regarding the correct diagnosis. The progression of her symptoms correlated both with her physical findings and with the progressive enlargement of her aneurysm as seen by roentgenograms. Her respiratory symptoms probably were secondary to compression of the bronchus of the left upper lobe by the aneurysmal mass. The progression of the dissecting aneurysm below the diaphragm was heralded by abdominal symptoms. Nineteen years after her initial dissection, the patient died of rupture of the aneurysm into the left pleural cavity.

Summary

The case history presented is believed to const tute the longest recorded survival of a patient with dissecting aneurysm that was diagnosed ant mortem. The patient lived for 19 years after th initial correct diagnosis.

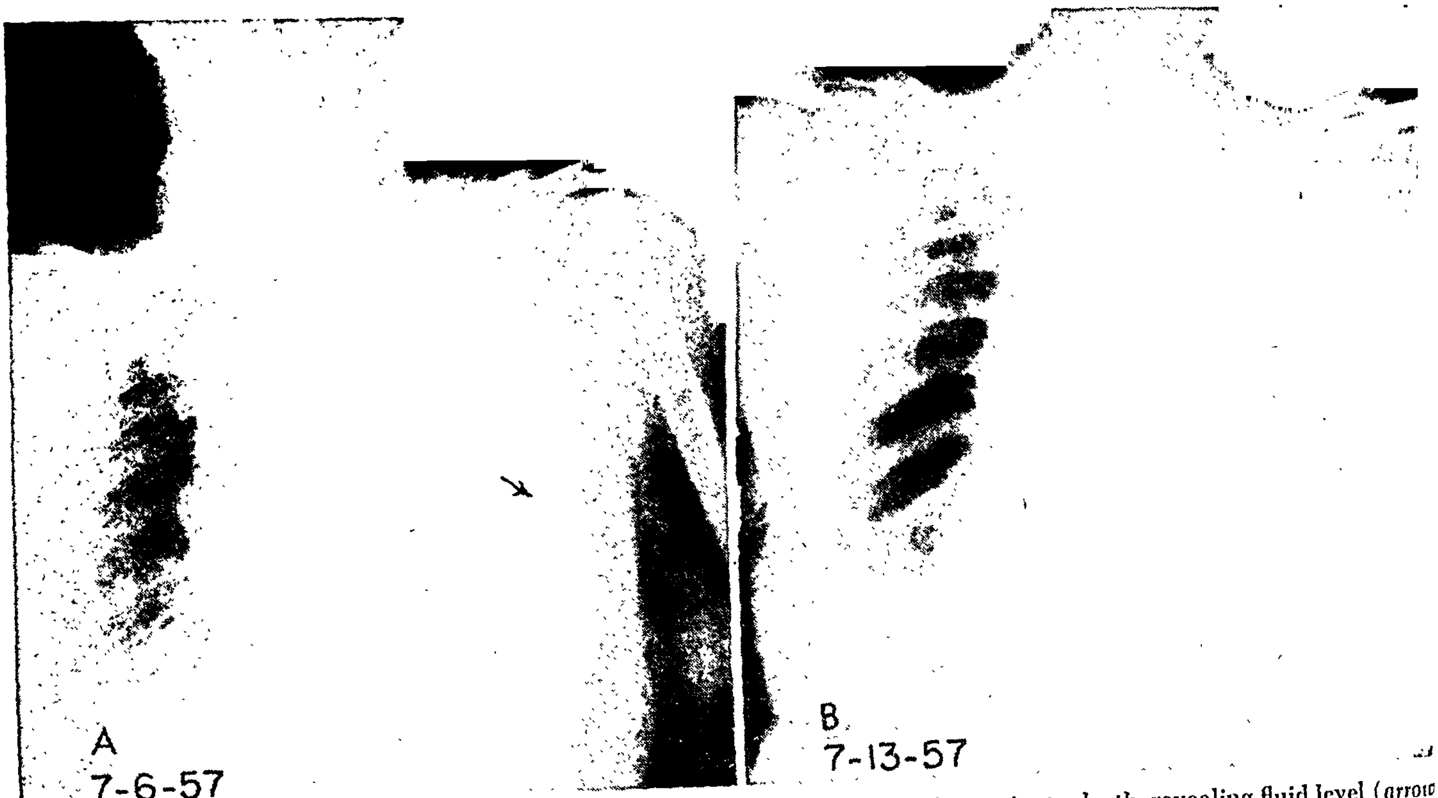

Fig. 3.—*A*, posteroanterior roentgenogram, recumbent position, taken eight days prior to death, revealing fluid level (*arrow*) below aneurysm. *B*, film taken one day prior to death, demonstrating obliteration of left pleural cavity by fluid.

Dr. Thomas T. Jones, Durham, N. C., made the original clinical diagnosis before referring this case to us, and Dr. William T. Futch, Jacksonville, N. C., furnished the roentgenograms and clinical records of the terminal illness.

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COMPLICATIONS AFTER RESECTION OF A RUPTURED ABDOMINAL ANEURYSM

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Resections of aneurysms of the abdominal aorta are being carried out successfully with increasing frequency. Elective operation with graft replacement can be a well-controlled procedure, with a low mortality. This is in contrast to the greater difficulty and risk involved in emergency surgery for a ruptured abdominal aortic aneurysm. Wider experience has served to emphasize the various complications that can be encountered. The aorta proximal to the aneurysm often is dilated and has a wall altered by advanced arteriosclerotic changes. The danger of suture line leak is considerably greater in these cases than in resection for segmental occlusive disease. The expanding aneurysm may encase a ureter in its dense fibrous wall and lead to obstructive uropathy. This fact is important in preoperative evaluation and, if possible, intravenous urography should be performed. In spite of adequate precautions, however, ureteral injury may occur at operation. The following case serves to emphasize some of the difficulties encountered in the diagnosis and treatment of a ruptured aneurysm of the abdominal aorta.

Report of a Case

History.—A 51-year-old man was admitted to the Jewish Hospital of Brooklyn on Oct. 3, 1958, because of lower abdominal pain of three weeks' duration and right leg pain for one day. In the past he had been treated for intermittent claudication and was reported to have had an elevated blood pressure for many years.

About three weeks prior to his hospitalization he experienced the onset of sticking lower abdominal pains. These persisted and began to radiate to the back. On the day before admission the pains became severe and extended into his right hip region, causing him to walk with a limp. This unrelenting pain forced him to seek hospitalization.

Examination.—Examination revealed the patient to be in acute distress. His temperature was 102.2 F (38.9 C), the pulse rate was 120 per minute, and the blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic. The abdomen was moderately distended. Palpation revealed marked spasticity and tenderness over the right upper and lower quadrants and right flank, and only mild tenderness over the left side. In the midabdomen an indistinctly outlined pulsating mass was felt. Both lower extremities were cool and presented no palpable pulsation. The admission blood count showed the hemoglobin concentration to be 11.4 Gm.%, the hematocrit reading was 33%, and leukocytes numbered 14,000 per cubic millimeter, with the differential count shifted markedly to the left. The urine contained some white blood cells and granular casts. The blood urea nitrogen level was 16 mg.%.

The clinical impression on admission was that the patient had a leaking abdominal aneurysm. One could not, however, exclude the possibility of right renal disease, such as a perinephric abscess or infected hydronephrosis. An emergency x-ray film of the abdomen demonstrated an opacity over the right side and linear calcification to the left of the lumbar spine. Intravenous urography (fig. 1) showed moderate dilatation of the right renal pelvis and upper ureter. The right ureter was deviated laterally and narrowed in its middle

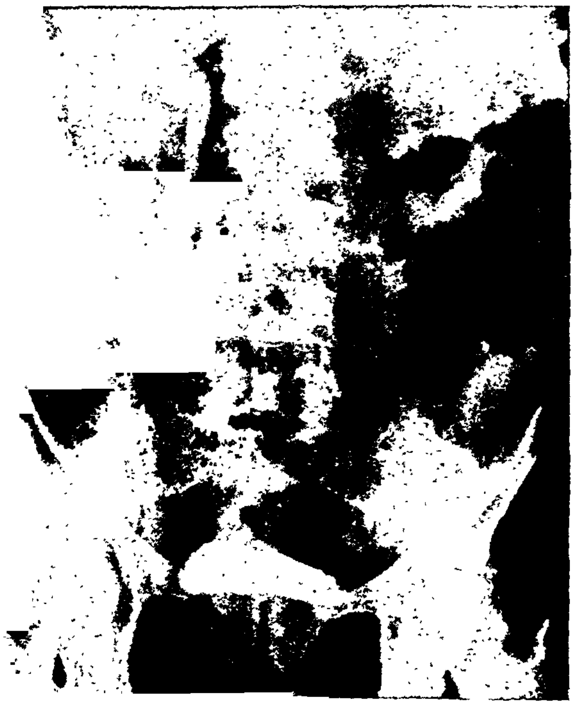

Fig. 1.—Complications of resection of ruptured aneurysm of abdominal aorta: intravenous urogram showing moderate dilatation of right renal pelvis and upper ureter. Right ureter is deviated laterally and narrowed in its middle third by abdominal aortic aneurysm.

From the Jewish Hospital of Brooklyn and the State University of New York, College of Medicine at New York City.

third by a retroperitoneal mass interpreted as an abdominal aneurysm. The electrocardiogram demonstrated evidence of myocardial ischemia and an old posterior wall infarct.

Operation.—The patient was subjected to cystoscopy preliminary to laparotomy. Two catheters were passed into the right renal pelvis and clear urine was obtained, thus excluding an infected hydronephrosis as the cause of the acute symptoms. The abdomen was then opened, revealing a huge retroperitoneal hematoma. It extended to the right of the midline, elevated the ascending colon, and surrounded the right kidney. The hematoma originated from an abdominal aneurysm which had ruptured on its right posterior aspect. The aneurysm extended from about 2 in. below the renal arteries to the level of the bifurcation of the aorta. Extensive arteriosclerotic changes were present in the proximal aorta and distal vessels. The right common iliac artery and its branches were completely occluded. On the left side, the common iliac and hypogastric arteries were patent, but the external iliac artery was a solid cord. Both common femoral arteries were exposed, but only the right side was found suitable for anastomosis. The abdominal aneurysm was then resected and replaced by an Edwards-Tapp bifurcation graft of crimped nylon. The distal limbs of the graft were anastomosed to the left common iliac and the right common femoral arteries.

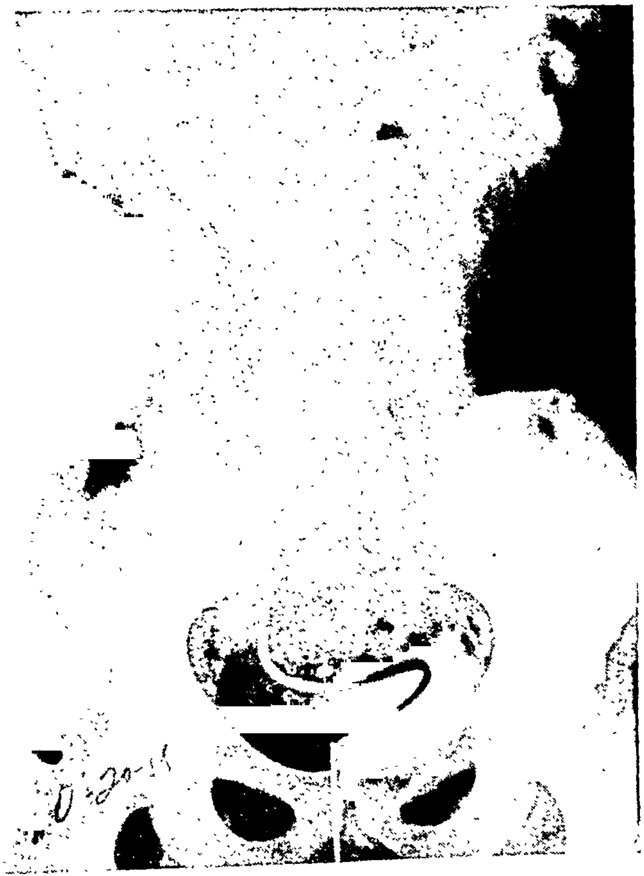

Fig. 2.—Retrograde catheterization of right ureter, demonstrating perforation of ureter at site of old injury by second catheter.

The wall of the aneurysm was extremely thick and fibrotic and encased the right ureter. During the course of dissection, the right ureter sustained a 2-mm. perforation, which was immediately closed with two sutures of 0000 chromic catgut.

Postoperative Course.—The patient's postoperative course was satisfactory after a transient episode of congestive failure that subsided with digitalization. The right ureteral catheters were removed on the seventh postoperative day, and one week later an intravenous pyelogram showed a residual hydronephrosis on the right. On the 15th postoperative day the patient's course was complicated by the appearance of hematuria. This was associated with tachycardia and a drop of the hemoglobin level to 11.6 Gm.%. The next d cystoscopy was carried out to investigate the cau of the bleeding. Bloody urine was visualized the bladder, coming from the right ureter. Wh a ureteral catheter was advanced up the rig ureter to the renal pelvis, however, clear uri was obtained. This localized the source of blee ing to the area where the lower right ureter w traumatized during operation. A second urete catheter was then inserted alongside the first o to effect dilation of the ureter, and an x-ray fi

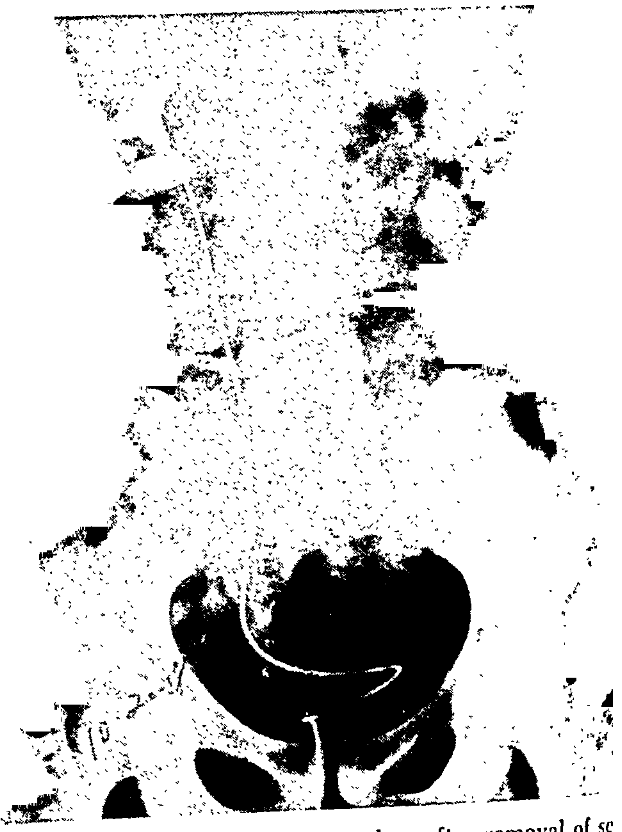

Fig. 3.—Retrograde pyelogram taken after removal of se ond catheter.

was taken again (fig. 2). This revealed that the second catheter had perforated the ureter at the site of the old injury and had been passed upward and to the left, to the region of the aorta-graft anastomosis. The second catheter was removed, and retrograde pyelography was then performed through the first catheter (fig. 3). This showed no leakage of dye into the retroperitoneal area.

During the ensuing week the patient had intermittent hematuria. His hemoglobin level and hematocrit reading remained stable, however, and the ureteral catheter was removed. On the 25th postoperative day he suddenly went into shock and was immediately taken to the operating room. Laparotomy revealed approximately 2,000 ml. of blood in the peritoneal cavity from a small leak at the proximal suture line. The leaking aortic anastomosis, together with a 1-in. segment of adjacent proximal aorta, was resected. This gap between the sclerotic aorta and the Edwards-Tapp graft was then bridged by inserting a polytetrafluoroethylene (Teflon) graft (fig. 4). It was noted at operation that a hematoma had dissected behind the mesentery of the small bowel into the retroperitoneal region near the right ureter. Thus, the hematuria present prior to this emergency procedure was caused by blood from a leak at the anastomotic site finding egress through the opening in the right ureter.

The patient made a satisfactory recovery from the second operative procedure. Both of his lower extremities were warm and had good arterial pulsations. He was recuperating satisfactorily until the 6th postoperative day (31 days after the initial procedure) at which time, while having a bowel movement, he suddenly collapsed and died.

Autopsy.—Postmortem examination revealed massive hemoperitoneum coming from a small perforation in the sclerotic aorta 1 cm. above the small polytetrafluoroethylene graft. Both anastomoses were intact. The site of injury to the right ureter showed evidence of healing. No other source of hematuria was found in the urinary tract.

Comment

A number of interesting facts were demonstrated by this case:

This patient's aneurysm may have been leaking slowly for three weeks and then bleeding rapidly prior to his hospitalization. Only a small percentage of patients die immediately from exsanguination when an aneurysm ruptures, and these usually perforate into the peritoneal cavity, stomach, or duodenum. The clinical state will obviously vary with the location and rapidity of the blood loss, but collected data indicate that most of these patients leak into their retroperitoneal region for hours or even days. A recent report by Bourne and Gaspar[1] emphasized that the interval between the onset of symptoms of rupture and death is usually over 10 hours. This is significant, since it indicates that in most cases there is adequate time after rupture to hospitalize the patient and carry out emergency surgery. If a diagnosis of retroperitoneal leak is made before the patient goes into collapse, the risk of intervention can be considerably reduced. Beebe and associates[2] discussed diagnostic aids that assist in the recognition of retroperitoneal bleeding. Pain in the back, flank, or hip regions may be the earliest signs of rupture, and there may be no complaints of abdominal pain.

Another interesting finding which this case demonstrated was that the clinical manifestations of a leaking abdominal aneurysm may be confused with other acute abdominal disorders. When this patient was hospitalized, he had fever and his abdomen was exquisitely tender and spastic over the entire right side and right flank. Palpation of a pulsating abdominal mass did not exclude the possibility of the existence of a second entity which could be responsible for the acute illness. Hemorrhage around a kidney may produce the signs and symptoms of an acute primary renal disorder, although the differential diagnosis must also exclude other diseases with acute abdominal findings, such as acute cholecystitis, pancreatitis, appendicitis, and mesenteric thrombosis.

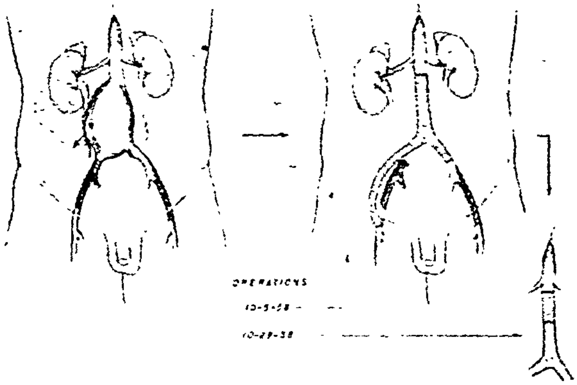

Fig. 4.—Drawing illustrating replacement of ruptured aneurysm by Edwards-Tapp graft and bridging of defect by polytetrafluoroethylene graft after resection of leaking proximal anastomosis.

The patient's right ureter was partially obstructed by the aneurysm. When such an aneurysm expands, it impinges on any retroperitoneal organ or vessel in its path. The adventitial layer of the aneurysm becomes thickened and may intimately involve the adjacent duodenum, vena cava, or ureters. In our case, the right ureter was obstructed as a result of displacement and encasement by the advancing wall of the aneurysm. The roentgenographic demonstration of ureteral compression is characteristic, showing the ureter coming to a fine tapering point. Reports in the literature [3] attest to the frequency of this urologic complication and emphasize the necessity for preoperative urography whenever possible.

The most unusual feature of this case was the demonstration that a slow leak from the aortic anastomosis could find egress through the site of ureteral injury. On the 15th postoperative day this patient had hematuria, which persisted without any significant fall in the hematocrit. Cystoscopy and right ureteral catheterization showed that the bleeding came from the retroperitoneal area through the hole in the right ureter. This explanation of the origin of the hematuria became apparent only later. The patient may have had a small anastomotic leak, which initially was confined to the retroperitoneal area for 10 days. This localized collection of blood was under enough pressure to produce leakage through the defect into the right ureter and did not allow extravasation of urine into the retroperitoneal area. Retrograde studies failed to demonstrate any leakage of injected contrast medium. This was probably due to a valve-like action at the site of ureteral injury.

Hemorrhage from a leaking suture line continues to be a major cause of operative death in patients with aortic aneurysm. This is usually due to the fact that the friable sclerotic host aorta does not hold sutures firmly, although intrinsic defects in grafts have been reported. The frequent occurrence of disproportion between aorta and graft contributes to suture line weakness. Our patient had advanced, diffuse arteriosclerosis, and the first anastomosis leaked because of necrosis at a point in the aorta at the suture line. One week after the second operative procedure he was exsanguinated from a perforation in the aorta above the suture line. Apparently, his sclerotic aorta could not tolerate the trauma of a vascular clamp. Shumacker [4] has also seen aortic perforation occur at the site of application of a clamp, and he recommends the use of less damaging occluding instruments.

The reported mortality for resection of ruptured abdominal aortic aneurysms is still high. Shumacker's series [4] had a 61.5% mortality, and Ellis and associates [5] reported a mortality of 35.4%. The results obviously will vary with the state of shock and exsanguination existing at the time of surgical intervention. This figure can be reduced, however, if one maintains a high index of suspicion and realizes that most ruptured aneurysms leak slowly enough to give the surgeon adequate time for intervention. DeBakey and associates [6] contrasted their 8% mortality in elective resections against the 33% mortality figure for resection of ruptured abdominal aneurysms. An asymptomatic aneurysm should be resected electively if the patient's general condition indicates a reasonable life expectancy. A symptomatic or enlarging abdominal aneurysm carries such a poor prognosis for immediate survival that resection should be undertaken even though the risk is great.

Summary

An aneurysm of the abdominal aorta may rupture into the retroperitoneum and produce symptoms that persist for hours or days before blood loss results in exsanguination. Prompt diagnosis and emergency resection can salvage many of these patients. The expanding fibrotic wall of an aneurysm may displace and encase the ureters, exposing them to injury during surgery. An unfortunate complication after anastomosis of a graft to an aorta with advanced arteriosclerotic changes is leakage at the suture line. Both of these complications occurred in the case reported by us. Blood in the retroperitoneum found egress through the site of ureteral injury and was manifested by hematuria.

10 Plaza St. (38). (Dr. Teicher).

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GRANULOCYTE SUPPRESSION WITH THIORIDAZINE HYDROCHLORIDE

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During 1957 and 1958 the department of psychiatry of the University of Minnesota Medical Center undertook an extensive clinical trial of a new phenothiazine derivative, thioridazine (Mellaril) hydrochloride, which was originally labeled TP-21. The chemical name for this drug is 2-methyl mercapto-10-[2-(N-methyl-2 piperidyl) ethyl]-phenothiazine.

An early report on it was by Fleeson and others.[1] Other investigators [2] have reported experiences with the same drug in a variety of psychiatric disorders. Our experience with the drug has been that it is one of the more satisfactory phenothiazine drugs, especially useful in controlling the symptoms of anxiety and agitation. This report is a description of the first agranulocytic reaction which has been encountered at the University of Minnesota Hospitals.

Report of a Case

A 54-year-old woman was admitted to the hospital because of an enlarging paranoid delusional system with gross distortions and misinterpretations of the tangled events of her life. In addition, the patient was visibly agitated, restless, and depressed. She complained of disturbed sleep and poor appetite. Her personal appearance, grooming, and orientation were in order.

There were no physical defects or abnormal findings at time of admission. Her pulse rate was 84 per minute and blood pressure was 120/78 mm. Hg. Results of chest x-ray and urinalysis were normal. The hemoglobin level was 13.7 Gm.% as determined by the oxyhemoglobin method. There were 9,050 white blood cells per cubic millimeter, with 60% polymorphonuclear cells, 36% lymphocytes, and 4% monocytes.

Twelve days after admission thioridazine was prescribed. Initially the patient received 150 mg. in divided doses. This dosage was increased over a four-day period to a total of 600 mg. per day and was continued.

On the 10th day after thioridazine was prescribed, the patient's temperature rose sharply to 103.2 F (39.4 C). She complained of diarrhea, stomach cramps, dizziness, and lassitude. Examination revealed no signs of illness except for moderate enlargement of the submandibular lymph nodes (not previously noted) and mild injection of the pharynx.

Throat culture and cultures of urine specimens revealed no pathogenic organisms. Through an error, no white blood cell count was made until four days after the appearance of fever and acute symptoms. At that time the total white blood cell count was 2,650 cells per cubic millimeter, with 40% polymorphonuclear cells, 59% lymphocytes, and 1% monocytes. The sedimentation rate, determined by the Westergren method, was 25 mm. in 60 minutes.

Phenothiazine drug therapy was discontinued after the report from the laboratory. On the second day after the drug therapy was stopped, the patient's temperature returned to 98.6 F (37.0 C) and remained normal for the next week. There was a gradual increase in total white blood cell count and a return to normal distribution of the cellular elements. Six days after phenothiazine therapy was discontinued, the laboratory reported a total white blood cell count of 7,050 per cubic millimeter, with 65% polymorphonuclear cells, 28% lymphocytes, and 7% monocytes. There were no significant variations from this during the next several days.

However, within two days after the drug therapy was discontinued, the patient's behavior changed markedly. Defensive and hostile trends, previously under control, recurred in the patient's verbal behavior. She became as overtly agitated as she was on admission and before drug therapy. The florid delusional system reappeared.

Recurrence of these symptoms required continuance of treatment. In addition, some of our consultants believed that fever, gastrointestinal disturbance, and depression of circulating granulocyte level might have been due to a virus infection. Therefore, thioridazine was again prescribed on the 36th hospital day, 10 days after it had been withdrawn and 6 days after the white blood cell count had stabilized at about 7,000 per cubic millimeter. She received 400 mg. of thioridazine daily for one week.

One day before drug treatment was ordered for the second time, the white blood cell count was 8,650 per cubic millimeter, with 66% polymorphonuclear cells, 30% lymphocytes, and 4% monocytes. After two days of drug treatment, the total count was 3,600, with 60% polymorphonuclear cells and

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From the Department of Psychiatry, University of Minnesota Medical Center.

32% lymphocytes. Although the total cell count remained about the same, the ratio of granulocytes to the lymphocytic series was reversed. On the last day of drug treatment the count was 4,500 total with 37% polymorphonuclear cells, 61% lymphocytes, and 2% monocytes.

After the drug was again withdrawn, the total white blood cell count decreased over a three-day period; the lowest reading was 2,650 per cubic millimeter. Within a week the differential ratio had returned to normal and the total count was 7,550 per cubic millimeter. Psychiatric symptoms returned as promptly as the granulocytes, and the severity of those symptoms required the use of other organic therapy (electroshock therapy).

Summary

Leukopenia occurring after treatment with the newer phenothiazine, thioridazine (Mellaril) hydrochloride, has been described. Because of doubt as to the offending agent, and because psychiatric symptoms returned when the drug was withdrawn, another course of drug therapy was instituted. There was prompt decrease in number of granulocytic elements in the blood stream a second time and equally prompt recovery to a normal blood cell count when the drug therapy was discontinued again. Other organic therapy was necessary to control the psychiatric symptoms. Thioridazine and other phenothiazine drugs can suppress the number of granulocytes. However, the suppression was neither permanent nor prolonged.

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QUADRIPLEGIA AFTER INTRATHECAL INJECTION OF METHYLENE BLUE

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and
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The absence of any case report in the literature on the subject of deleterious effects of methylene blue injected intrathecally prompted us to report this case study as a warning. The only reference[1] we have found is a letter by Evans warning against its use. His report dealt with a patient who developed paraplegia and almost completely recovered.

Report of a Case

A 21-year-old woman was in an automobile accident on Aug. 16, 1958. She fell asleep momentarily while driving her automobile, which struck a lamp post. She remained conscious after the accident and was treated as an outpatient for abrasion over the bridge of the nose, hematoma of the right forearm, discoloration of both eyes, and Bennett's fracture of the left thumb.

Five days later, she was hospitalized for observation of supposed rhinorrhea. On Aug. 28, spinal fluid examination revealed a total protein level of 38 mg.%, with no cells. To rule out a cerebrospinal rhinorrhea, 1 cc. of methylene blue, 1% aqueous solution, was injected into the lumbar subarachnoid space. Fifteen minutes after the injection, the patient experienced pain and tingling in the lower extremities and began to hyperventilate. Carpopedal spasm was also present, but that and the tingling were relieved by rebreathing into a paper bag. However she was unable to move the lower extremities and showed symptoms of diplopia. She was unable to void, so an indwelling catheter was inserted.

On Aug. 29, the sensory examination gave normal results, but motor examination revealed only feeble toe movements. All the extremities were areflexic. On Sept. 1, the patient was able to move the toes, ankles, and knees, though not against resistance. On Sept. 3, all motion in the lower extremities had disappeared and she developed a partial sensory loss below the nipple line. On Sept. 4, the patient was given 500 mg. of amobarbital (Amytal) sodium intravenously to reduce apprehension and a repeat lumbar puncture was performed. The initial pres-

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sure was 300 cm. H_2O. The clear, colorless, fluid revealed 192 mg.% protein with 16 cells per cubic centimeter; 95% of the cells were lymphocytes and 5% were polymorphonuclear leukocytes. The spinal fluid culture gave negative findings. A myelographic study was performed on Sept. 5 which revealed no indication for decompressive laminectomy.

The patient was started on hydrocortisone therapy on Sept. 7. By Oct. 15 her sensory level dropped to 3 in. below the nipple line and cortisone therapy was discontinued. About Oct. 20, the right internal strabismus, which had been present since Aug. 28, became more intense. The fuzziness of the disk margins, which had been present since the middle of September, suddenly became pronounced. On Oct. 22, the patient noted severe diminution of vision, especially in the right eye.

On Oct. 28, bilateral occipital bur holes were made and the left lateral ventricle was tapped. The fluid was under increased pressure but was clear. Examination of the cerebrospinal fluid revealed 7 mg.% protein with one leukocyte per cubic centimeter. Ventriculography revealed symmetrical dilatation of all ventricles.

During the night of Oct. 28, the patient became completely blind. A ventriculogram on Oct. 29, performed under general anesthesia, revealed advanced internal hydrocephalus and filling of the fourth ventricle; however, there was no filling of the subarachnoid space. On Oct. 31, a right ventricular–right auricular shunt was performed with a Holter tube. Postoperatively, the patient developed a toxic-type psychosis with confusion, restlessness, and hallucinations.

She was transferred to the Veterans Administration Hospital on March 6, 1959, with diagnoses of encephalomyeloneurarachnoidopathy, secondary to intrathecal methylene blue injection; paralysis of the lower extremities with incontinence of bladder and bowel; impaired visual acuity; and headaches, nausea, and vomiting.

Chest x-rays, pyelograms, and an upper gastrointestinal series showed normal findings. X-rays taken of the skull taken on March 6, revealed bilateral bur holes, and there were a few driplets of cophendylate (Pantopaque) in the basal cisterna. There were two adapters overlying the right parietotemporal portion of the calvarium. The pineal gland was not calcified, and the sella turcica appeared normal.

An electroencephalogram taken on March 16 showed basic 9 per second activity with some fast 20 to 25 per second frequencies in the frontal and parietal leads. There were several paroxysmal bursts with generalized slow six per second activity.

Viral blood studies performed on April 3 and April 14 gave negative results for Eastern, Western, and St. Louis types of equine encephalomyelitis and Japanese encephalitis. Three attempts at spinal manometric determination performed at different lumbar levels by two operators were unsuccessful.

Eye examination on April 3 showed vision in the left eye to be 20/30, but the patient missed the letters on her left. The impression was that the patient had simple optic atrophy of the right eye and possibly early atrophy of the left disk.

On April 24, a small bladder stone was removed. Electromyographic examination on April 20 revealed that the right tibialis anticus, peronei, gastrocnemius, and right and left first dorsal interosseous muscles showed electrical signs of lower motor neuron lesion by elevation of chronaxy, failure to respond to stimuli of short duration, and faradism.

At the time of this writing the patient had no sense of smell. She was able to distinguish fingers of the hand about 3 or 4 in. from the right eye and shadows at about 4 to 5 ft. There was a slight internal strabismus of the right eye.

In the upper extremities, the deltoids, biceps, and brachioradialis muscles contracted fairly well. The triceps contracted against gravity but were weak against resistance. She was able to lie in supine and prone positions fairly well and was able to flex and extend the wrists against gravity, but hand grips were weak. Adduction and abduction of the fingers were performed weakly and opponens action was also weak. She was able to flex and extend the fingers weakly. The thoracic musculature was paralyzed below T-3. The abdominal muscles and both lower extremities were paralyzed, and the patient had an indwelling urethral catheter.

Pain and temperature sensations were absent from about the second rib downward, without sacral sparing. Light touch sensation was absent from T-4 down and decreased from T-2 to T-4. Vibratory sensation was absent from the lowermost ribs downward. Deep pressure and position sense were absent in the lower extremities. The patient also had some loss of pain and temperature sensation over the medial surface of the right arm and forearm and over the fourth and fifth fingers; light touch was decreased over these areas.

The biceps reflexes were elicited bilaterally; the left was stronger than the right. The triceps reflexes were questionable. The radial and ulnar reflexes were elicited bilaterally, and the left radial was plus minus. No Hoffman sign was present. Abdominal reflexes were absent, and there was complete areflexia in the lower extremities. No pathological toe signs were obtained.

Summary

A young woman suffered a mild head injury without unconsciousness after an automobile accident. Because of the complaint of rhinorrhea 12 days after the accident, an aqueous solution of methylene blue was injected intrathecally to rule out cerebrospinal rhinorrhea. Fifteen minutes later she developed an ascending paraplegia with evidence of peripheral nerve root and spinal cord involvement. The spinal fluid showed evidence of inflammatory reaction with marked elevation of protein level. The patient gradually developed cerebral signs which necessitated decompression with a Holter tube for purposes of cerebral decompression. At the time of this writing she had bilateral optic atrophy, anosmia, and quadriplegia. The lower extremities were severely paralyzed and flaccid.

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ANAPHYLACTIC REACTION TO AQUEOUS CHYMOTRYPSIN INJECTION

DEVELOPMENT IN A PREVIOUSLY NONSENSITIVE PATIENT

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For several years the protease chymotrypsin has been among the available adjunctive treatments for traumatic injuries in which tissue hemorrhage and edema present a problem.[1] The toxicity of this material has been studied, and it has been found to be relatively nontoxic.[2] However, being protein in nature it might be expected to elicit a sensitivity reaction in susceptible persons. A survey of the literature revealed a report on only one such sensitivity reaction.[3] This note constitutes a report of a reaction to aqueous chymotrypsin (Chymar) in which sufficient sensitivity was built up over nine days to produce serious anaphylactic shock.

Report of a Case

The patient was a 19-year-old man who was admitted to the University Health Center on Oct. 17, 1959, after an acute facial injury sustained in varsity football competition. A diagnosis of multiple fractures of the right maxilla was made. Because of intense edema, ecchymosis, and antrum hemorrhage which precluded immediate reduction of the fractures, he was treated with ice packs and the deep intramuscular injection of 1 cc. (5,000 units) of aqueous chymotrypsin every 12 hours. Prior to injection, an intradermal skin test was done, with a negative result. Ancillary treatment in the form of oxytetracycline with glucosamine (Cosa-Terramycin), meperidine (Demerol) hydrochloride, and an acetylsalicylic acid, acetophenitidin, and caffeine (Empirin) compound with codeine was given. Because of the history of a reaction to tetanus antitoxin injection when a small boy, tetanus immunization was not given in any form. The patient's history was free from any other reference to allergic manifestations.

By the third day the edema and ecchymosis had subsided sufficiently to allow reduction of the fractures, and the patient was transferred to one of the local general hospitals where this was accomplished. He returned to the university hospital on the sixth postinjury day and continued to receive treatment with aqueous chymotrypsin, 1 cc. daily. On the eighth day, having received his 10th injection, he complained of some itching and inflammation about the injection site. When he was examined on the next morning nothing was seen, and the order for the chymotrypsin injection was not discontinued. The 11th and last injection was given at 10 a.m. on Oct. 25, 1959. Symptoms of uneasiness began almost at once, and by 10:10 a.m. the patient was pulseless.

He was first seen at 10:15 a.m. and was in profound shock and cyanotic, complaining of dyspnea and with an urgency to void but an inability to do so. Complaints of precordial pain were prominent. One ampul (1 cc.) of epinephrine in oil had been administered and oxygen was being given at 7 liters per minute by face mask. One hundred milligrams of hydrocortisone sodium succinate (Solu-Cortef) was given intravenously immediately. The apical beat was between 120 and 140 per minute, peripheral pulses were unobtainable, and blood pressure readings were zero. In five minutes the picture had somewhat worsened, dyspnea becoming more apparent with the appearance of phlegm in his throat. His lungs sounded clear, but 2 cc. of caffeine sodium benzoate was administered hypodermically. Carpopedal spasm was apparent and the oxygen mask was removed. From then on, oxygen was administered by suspension of the mask over his face.

By 10:40 a.m. his breathing was easier, a blood pressure reading of 60/0 mm. Hg. was obtained, but no peripheral pulse was palpable. A second 100 mg. of hydrocortisone sodium succinate was given intravenously. His color gradually returned to normal and by 12 noon his blood pressure was 110/80 mm. Hg, pulse rate 86 per minute, and respirations 18 per minute. His symptoms of chest

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pain and urinary urgency were gone. Oral corticosteroid treatment was instituted. At 4:30 p.m. the patient stated, "I feel the best I have felt since I came back from surgery." He attended classes the next day and has been completely well since. Oral corticosteroid therapy was continued for six days in decreasing doses.

On the fourth day after his anaphylactic shock, a drop of aqueous chymotrypsin was placed on his forearm and a few minimal pressure points were made with a vaccination needle. He developed a reaction showing a zone of erythema measuring 2 in. and a wheal measuring 1 cm. in diameter.

A summary of the case reveals that the patient had a negative result of an intradermal test for Aqueous Chymar. He received 11 1-cc. injections of this substance, all in the buttocks, over a period of nine days; developed a local irritation at the site of injection on the eighth day, which disappeared spontaneously; and then went into profound anaphylactic shock within 10 to 15 minutes after the last injection.

Streptokinase-streptodornase (Buccal Varidase), the only other possible irritant, was given at 8 a. m., two hours and 15 minutes preceding the onset of the anaphylactic reaction. Recovery was relatively prompt after administration of epinephrine and injection of a soluble corticosteroid preparation. A recent report states that "intravenous administration of steroid preparations is of no avail in the control of an immediate reaction."[4] On the contrary, I believe that this material was lifesaving, in view of this patient's previous traumatic and surgical stress. The patient was completely recovered within a few hours.

Summary

Serious anaphylactic shock resulted from intramuscular injections of aqueous chymotrypsin (Chymar). Sensitivity was built up over eight days. Recovery was prompt and complete after the use of epinephrine, oxygen, and an intravenous soluble corticosteroid preparation.

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PREANESTHETIC MEDICATION WITHOUT NARCOTICS

USE OF PROMETHAZINE AND A SYMPATHOMIMETIC AGENT IN 5,500 PATIENTS

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Preanesthetic medicaments are administered for one or more of several reasons: (1) to relieve apprehension, (2) to supplement the anesthetic, (3) to relieve pain, and (4) to control vomiting. Many modifications of standard techniques have been studied in an effort to provide more adequate relaxation with greater safety. The classic preoperative combination included morphine and scopolamine hydrobromide or atropine, usually in a ratio of 25:1.[1] However, with the advent of more potent anesthetic agents, it was soon realized that heavy medication before operation was neither desirable nor necessary. Administration of a mixture of depressant compounds, as an oral barbiturate [2] and a narcotic, for preoperative sedation, and an ultrashort-acting barbiturate for induction, followed by administration of one of the modern anesthetics, frequently produced results entirely disproportionate to the requirements of the patient.

The pendulum of clinical thought then swung to the opposite end of the scale, and few or no premedicants were used. However, preoperative sedation is recognized as essential to the management of the surgical patient, and it became apparent that the principles of anesthesiologic practice could not be so radically altered merely on the basis of disappointing clinical experience.

New Concept

On introduction of the ataractic compounds, particularly the agents with more or less antihistaminic effect, a new concept developed concerning the results obtainable with preoperative medication. For the first time it seemed possible to achieve reduction of the metabolic rate and some degree of cerebral sedation without cardiovascular depression or adverse effect on the compensatory mechanisms. Some of these compounds, however, failed to provide the desired degree of quiescence,[3] others produced an undesirable depression, and some proved completely ineffectual for given 75 mg. per example, various members sulfamethoxypyridazine group possess a divergitis. After three doses (48-72 ertic and in clin slightly papular, deeply erythe-

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days after the accident, an aqueous solution of methylene blue was injected intrathecally to rule out cerebrospinal rhinorrhea. Fifteen minutes later she developed an ascending paraplegia with evidence of peripheral nerve root and spinal cord involvement. The spinal fluid showed evidence of inflammatory reaction with marked elevation of protein level. The patient gradually developed cerebral signs which necessitated decompression with a Holter tube for purposes of cerebral decompression. At the time of this writing she had bilateral optic atrophy, anosmia, and quadriplegia. The lower extremities were severely paralyzed and flaccid.

670 Michigan Ave., Chicago (Dr. Arieff).

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ANAPHYLACTIC REACTION TO AQUEOUS CHYMOTRYPSIN INJECTION

DEVELOPMENT IN A PREVIOUSLY NONSENSITIVE PATIENT

Kenneth D. Rose, M.D., Lincoln, Neb.

For several years the protease chymotrypsin has been among the available adjunctive treatments for traumatic injuries in which tissue hemorrhage and edema present a problem.[1] The toxicity of this material has been studied, and it has been found to be relatively nontoxic.[2] However, being protein in nature it might be expected to elicit a sensitivity reaction in susceptible persons. A survey of the literature revealed a report on only one such sensitivity reaction.[3] This note constitutes a report of a reaction to aqueous chymotrypsin (Chymar) in which sufficient sensitivity was built up over nine days to produce serious anaphylactic shock.

Report of a Case

The patient was a 19-year-old man who was admitted to the University Health Center on Oct. 17, 1959, after an acute facial injury sustained in varsity football competition. A diagnosis of multiple fractures of the right maxilla was made. Because of intense edema, ecchymosis, and antrum hemorrhage which precluded immediate reduction of the fractures, he was treated with ice packs and the deep intramuscular injection of 1 cc. (5,000 units) of aqueous chymotrypsin every 12 hours. Prior to injection, an intradermal skin test was done, with a negative result. Ancillary treatment in the form of oxytetracycline with glucosamine (Cosa-Terramycin), meperidine (Demerol) hydrochloride, and an acetylsalicylic acid, acetophenitidin, and caffeine (Empirin) compound with codeine was given. Because of the history of a reaction to tetanus antitoxin injection when a small boy, tetanus immunization was not given in any form. The patient's history was free from any other reference to allergic manifestations.

By the third day the edema and ecchymosis had subsided sufficiently to allow reduction of the fractures, and the patient was transferred to one of the local general hospitals where this was accomplished. He returned to the university hospital on the sixth postinjury day and continued to receive treatment with aqueous chymotrypsin, 1 cc. daily. On the eighth day, having received his 10th injection, he complained of some itching and inflammation about the injection site. When he was examined on the next morning nothing was seen, and the order for the chymotrypsin injection was not discontinued. The 11th and last injection was given at 10 a.m. on Oct. 25, 1959. Symptoms of uneasiness began almost at once, and by 10:10 a.m. the patient was pulseless.

He was first seen at 10:15 a.m. and was in profound shock and cyanotic, complaining of dyspnea and with an urgency to void but an inability to do so. Complaints of precordial pain were prominent. One ampul (1 cc.) of epinephrine in oil had been administered and oxygen was being given at 7 liters per minute by face mask. One hundred milligrams of hydrocortisone sodium succinate (Solu-Cortef) was given intravenously immediately. The apical beat was between 120 and 140 per minute, peripheral pulses were unobtainable, and blood pressure readings were zero. In five minutes the picture had somewhat worsened, dyspnea becoming more apparent with the appearance of phlegm in his throat. His lungs sounded clear, but 2 cc. of caffeine sodium benzoate was administered hypodermically. Carpopedal spasm was apparent and the oxygen mask was removed. From then on, oxygen was administered by suspension of the mask over his face.

By 10:40 a.m. his breathing was easier, a blood pressure reading of 60/0 mm. Hg. was obtained, but no peripheral pulse was palpable. A second 100 mg. of hydrocortisone sodium succinate was given intravenously. His color gradually returned to normal and by 12 noon his blood pressure was 110/80 mm. Hg, pulse rate 86 per minute, and respirations 18 per minute. His symptoms of chest

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From the University Health Service, University of Nebraska.

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ERYTHEMA MULTIFORME EXUDATIVUM ASSOCIATED WITH USE OF SULFAMETHOXYPYRIDAZINE

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The observation of three cases of erythema multiforme exudativum (Stevens-Johnson Syndrome) associated with the administration of sulfamethoxypyridazine (Kynex) and the knowledge of at least two other instances observed by others prompted this communication. It is always difficult to statistically validate the side-effects of a widely used drug with a low incidence of toxicity. However Craven's[1] recent experience with one case, Lindsay's[2] observation of three cases, and the five cases in this report suggest that erythema multiforme exudativum may occur as a reaction to sulfamethoxypyridazine with greater frequency than previously reported for other sulfonamide preparations.

Report of Cases

Case 1.—A 1½-year-old boy who weighed 28 lb. (12.7 kg.) and had a history of mild otitis media of two days' duration was treated with 375 mg. of sulfamethoxypyridazine daily. On the second day of therapy, an erythematous maculopapular eruption appeared. Vesiculation of the skin lesions, vesiculo-desquamation of the oral mucosa, severe conjunctivitis, and urethritis with dysuria appeared on the third day. A diagnosis of erythema multiforme exudativum was made. The pyrexia, toxicity, and skin lesions seemed to respond to steroid therapy. However, friable, bleeding lesions of the oral mucosa continued for several weeks. The amount of sulfamethoxypyridazine administered was within the advised range of dosage (250 mg. per 20 lb. of body weight). No other medicament was given. On previous occasions, sulfisoxazole (Gantrisin) had been administered without incident.

Case 2.—An 8-year-old girl who weighed 56 lb. (25.4 kg.) was treated with sulfamethoxypyridazine for bilateral otitis media. A daily dose of three teaspoons (750 mg.) was prescribed. No other medicament was given. On the seventh day of therapy the temperature suddenly increased to 105 F (40.6 C) and marked irritability and prostration occurred. An erythematous eruption which had appeared the previous day had become vesicular. The mucous membranes of the mouth and vagina were edematous, erythematous, and friable. Severe conjunctivitis and photophobia rapidly ensued. In scattered areas the lesions of the skin coalesced to form bullae. Response to steroids was adequate, but it was complicated by periods of urinary retention due to recurrent vaginourethral lesions. The onset and clinical course of the lesions in this patient were classic for erythema multiforme exudativum.

Case 3.—A 28-year-old man had been taking 0.5 Gm. of sulfamethoxypyridazine daily for three weeks for persistent symptoms of an upper respiratory infection. On the 22nd day of therapy, a faint scattered maculopapular eruption appeared, followed by vesicular lesions of the buccal mucosa which quickly desquamated. On the next day, temperature suddenly rose to 104 F (40.0 C) associated with severe prostration. The maculopapular eruption had become intensely erythematous, involved the entire skin surface, and progressed rapidly to vesiculation and bullous formation. The palpebral, ocular, urethral, and anal mucous membranes displayed a vesiculodesquamating inflammatory reaction. After cessation of the drug therapy, and after intensive electrolyte and steroid therapy, profuse desquamation of the skin lesions and subsequent healing occurred. The lesions of the conjunctivae, however, were slow in resolving. No other drugs had been taken nor was there any doubt as to the diagnosis of erythema multiforme exudativum.

Case 4.—A 4½-year-old girl was given 75 mg. per kilogram of body weight of sulfamethoxypyridazine daily for mild pharyngitis. After three doses (48-72 hours) a macular, slightly papular, deeply erythe-

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From the Department of Pediatrics, New York University Bellevue Medical Center.

matous rash appeared on the face, trunk, and extremities. and the temperature rose to 105 F (40.6 C). After 12 hours, bullous lesions appeared on the buccal mucosa, the palpebral conjunctivae were inflamed, the urethral orifice was swollen and erythematous, and the patient complained of dysuria. The drug was withdrawn, and, after seven days of symptomatic therapy, the skin and mucous membrane lesions gradually subsided. In this instance, the administered dose of sulfamethoxypyridazine was at least three times the advised amount.

CASE 5.—A 9-year-old girl was seen in the emergency room for what was described later as an attack of asthma. She was treated with ephedrine, and 400,000 units of penicillin daily for four days was prescribed, along with cough syrup and 2 tablets of sulfamethoxypyridazine the first day and 1 tablet daily thereafter. After 13 days of sulfamethoxypyridazine therapy, a slight rash appeared over the face, associated with a sore throat. A diagnosis of measles was considered. This eruption faded, but two days later there was marked pruritus over the arms and legs and about the eyes. The next day, vesicular lesions appeared on the oral mucosa, and a rapidly-spreading maculopapular erythematous rash appeared on the arms, legs, and trunk, with scattered areas of vesiculation. There was marked conjunctivitis, with suffusion and photophobia. The skin lesions progressed from vesicles to huge bullae, with ultimate desquamation of large areas of the skin. In spite of vigorous electrolyte and steroid therapy, the patient died on the 12th hospital day. The clinical picture and skin and mucous membrane lesions in this case were believed consistent with a diagnosis of severe erythema multiforme exudativum. Unfortunately, it was difficult in this case to assess the possible influence of penicillin administered two weeks prior to the onset of the fatal toxic reaction.[3]

Comment

There are pitfalls in attributing a causal relationship to a drug in a syndrome of unknown etiology such as erythema multiforme exudativum. It may be argued that (1) all these cases are pure coincidence; (2) the symptoms for which the drug was prescribed in the first place represented the prodrome of a primary syndrome; and (3) other concurrent agents or factors are at fault. Sulfonamide preparations have been previously implicated as sensitizing agents for erythema multiforme exudativum. The decision about whether there is an increased incidence of such sensitization after sulfamethoxypyridazine therapy cannot be made until further experience and awareness have been acquired. However, the serious nature of the toxic manifestations (one death out of the five cases reported here) may warrant more critical evaluation of the use of the drug.

Addendum

Since the preparation of this article, Garner[4] has observed erythema multiforme exudativum associated with the administration of sulfamethoxypyridazine in three children.

550 First Ave. (16).

Dr. C. W. Daeschner, of Baylor University, Texas, gave permission to report case 5.

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SPINAL FLUID ELECTROPHORESIS PATTERN OF A PATIENT TREATED WITH TRIFLUPROMAZINE

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Triflupromazine hydrochloride (Vesprin), a phenothiazine preparation, has been prescribed for patients with anxiety tensions.[1] The case to be reported here is the first in which toxic symptoms have occurred. The dosage in this case was small and given for a short period of time. The toxic symptoms of extrapyramidal disease were severe. Cerebrospinal fluid protein electrophoretic patterns were obtained, and the results were unusual.

Report of a Case

A 21-year-old housewife was referred to me in the course of an emotional crisis in her family. Meanwhile, her physician had advised the use of triflupromazine. The dosage, according to her physician, was two 10-mg. tablets daily for about three weeks prior to my examination. The patient related the following progression of symptoms: shortening of her step leading to a shuffling gait, impairment of motion and movement, a feeling that she was "not able to get about," and a sensation that she

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was a bit "foggy." Associated with these symptoms was an excessive amount of vaginal bleeding. At the time of her examination, the findings were essentially normal except that the blood cell count showed 11 Gm. of hemoglobin per 100 cc. A gynecologist found no obvious cause for the vaginal bleeding and suggested that it was due to endometrial hyperplasia secondary to the anemia, which might well have been an additional toxic manifestation of the triflupromazine. Neurological examination disclosed the classic symptomotology and findings of parkinsonism. There was rigidity of her long muscles of the cogwheel and lead type. She had definite bradykinesia and inability to smile readily. There was masked facies, increased globus, and postural changes. She also had a resting pill-rolling type of tremor.

The drug therapy was continued during the early period of hospitalization, lumbar puncture was performed, and skull and chest x-rays were taken. The x-rays showed findings within the limits of normal. The lumbar puncture revealed normal fluid dynamics. The cerebrospinal fluid chemistry showed the following results: protein level, 18 mg.%; negative result of Pandy test; sugar level, 64 mg.%; colloidal gold curve, 0012100000; and a nonreactive result of Kahn test. Electrophoretic study revealed a reversal of albumin-globulin ratio; albumin level was 33% and globulin level 67.3%, a ratio of 1:2 (fig. 1).

Triflupromazine therapy was discontinued, and the patient was sent home without other therapy. When she was readmitted to the hospital six weeks later, a lumbar puncture revealed normal intraspinal dynamics. Cerebrospinal fluid chemistry findings were reported as follows: protein level, 19 mg.%; and colloidal gold curve, 0001000000. The electrophoretic pattern was repeated and continued to show a slightly elevated betaglobulin value, although in general the pattern was returning to normal (fig. 2). The albumin level was 59% and the globulin level 41% (an approximate ratio of 3:2).

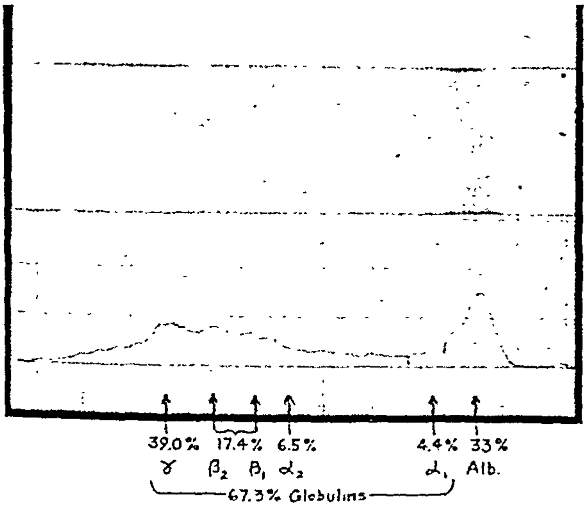

Fig. 1.—Total protein level, 18 mg. %. First spinal fluid was taken while patient was taking triflupromazine hydrochloride.

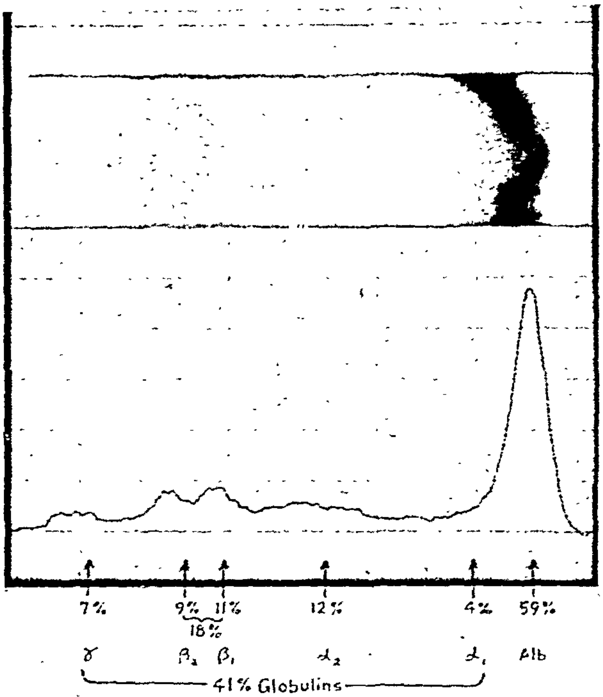

Fig. 2.—Total protein level, 19 mg. %. Patient had not been taking tranquilizers for six weeks.

Comment

Shaw and co-workers[2] reported 9 cases of phenothiazine compound intoxication and referred to 10 additional observed cases.[3] Their review of the literature made no reference to cerebrospinal fluid protein electrophoretic patterns. Other reviews have not mentioned cerebrospinal fluid findings, although extrapyramidal changes are noted by all who have dealt with these drugs.

The cerebrospinal fluid protein analysis by electrophoresis was performed as part of a general study. The technique for obtaining electrophoretic cerebrospinal fluid protein analysis was as follows. The method used here was paper chromatography. To obtain an analysis, the cerebrospinal fluid was concentrated through a dialysis.[4] The cerebrospinal fluid was concentrated 50 to 100 times by dialyzing 5 to 10 cc. of spinal fluid against a 30% solution of polyvinylpyrollidone solution containing 0.9% sodium chloride and a crystal of thymol as a preservative. The material was dialyzed overnight in a refrigerator. About 0.1 cc. of concentrated spinal fluid was obtained.

Electrophoresis.[4]—The proteins in the concentrate were separated by electrophoresis. This was carried out on the Spinco apparatus with a barbital buffer of 0.075 ionic strength and pH 8.6. Either 0.01 or 0.02 cc. of spinal fluid concentrate, depending on protein concentration, can be placed on the electrophoresis paper. The grade of paper used was Schleicher and Schuell 2043-A. The electrophoresis proceeded for about 16 hours at a current strength of 2.5 ma. At the end of that time, the papers were dried at a temperature of 120 to 130 C (248 to 266 F), stained according to the Spinco procedure B, washed in methanol, and then stained with brom thymol blue for one-half hour. They were decolorized with three rinses of 5% acetic acid solution and dried. The color of the dye was intensified by exposure to ammonia vapors, and the intensity of dye was measured in the Spinco analytrol apparatus.

These pattern changes of protein content in the spinal fluid raise the following questions as to their significance: were these changes representative of toxic effects on the cellular permeability at the blood brain barrier, thus allowing for the albumin-globulin ratio reversal, or was this a poisoning effect to the neurons of the extrapyramidal portion of the brain known as the striopallidal system? The effects caused damage to the cerebral tissues and altered the metabolic processes which allowed for the pattern change. This latter point seems more likely in view of the pathology observed in the brain associated with viral, carbon monoxide, and other toxins that effect the striopallidal system.[1]

It seemed that this would indicate that phenothiazine drugs had a direct neuronal toxic effect caused in a chemical biotaxic manner to indicate a neural affinity for these specific neurons.

Summary

A case of triflupromazine hydrochloride (Vesprin) intoxication produced extrapyramidal symptoms which resulted in a curious dissociation of cerebrospinal fluid protein pattern and albumin-globulin ratio shifts. With the removal of the toxins, these changes seemingly were reversed.

516 Sutter St.

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NEUROLOGICAL COMPLICATIONS OF ANTIRABIES VACCINE

TREATMENT WITH CORTICOSTEROIDS

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and
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Neuroparalytic complications occur in 1 of every 287 to 1 of every 8,287 persons receiving the Pasteur antirabies vaccine.[1] Greenwood [2] found an over-all incident of one reaction to 5,814 treatments on a world-wide basis in a total series of 1,297,758 treated patients. In the same series, there were 56 fatalities, equivalent to 25% mortality in those suffering a neuroparalytic complication. Latimer and co-workers [1] reported 40% mortality in 22 cases of neurological complication reported in the literature. A rabies vaccine prepared from virus grown on duck embryo is now available from commercial sources. This preparation will materially reduce the use of vaccine prepared from rabbit central nervous system.[3] However, certain persons may not be able to tolerate the avian embryo vaccine, so it seems unlikely that the rabbit central nervous system preparation (Pasteur vaccine) will fall into complete disuse.[4] A person with a severe neuroparalytic reaction to the Semple-type vaccine (rabbit central nervous system preparation inactivated with phenol) was recently treated with corticosteroids. It is believed the dramatic response of this potentially lethal effect to the corticosteroids merits reporting.

Report of a Case

A 24-year-old man was bitten by a dog which could not be found. Treatment was started consisting of a 14-day course of rabies vaccine in accordance with the World Health Organization recommendation. The Semple-type vaccine was used. The patient developed anorexia, marked pain, and swelling at the site of injections after the sixth injection, but treatment was continued until he was

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admitted to the hospital on the 12th day with prostration and dehydration. No neurological deficit had been noticed up to this time.

Physical examination at the time of admission revealed normal vital signs; however, the patient appeared acutely ill, dehydrated, and quite pale. Except for questionable hypalgesia of the left leg, the results of the neurological examination were normal. There were no other physical abnormalities. The only significant laboratory finding was a leukocyte count of 16,250 with 79% neutrophils and 5% eosinophils.

Therapy was started with intravenously given fluids and analgesics. However, it soon became apparent that the patient's condition was growing progressively worse. Twenty-four hours after admission, there was complete urinary retention, dysarthria, and paresthesias of the face, neck, and arms. Lumbar puncture revealed a normal spinal fluid pressure, pleocytosis with a count of 21 lymphocytes and 29 red blood cells, and a protein level of 56 mg.%. During the second day of hospitalization, abdominal, cremasteric, and gag reflexes disappeared. The patient continued to regress during the next 24 hours to a state of profound, generalized weakness with complete loss of voluntary muscle contraction of both lower extremities, loss of pain sensation over the lower limbs, and definite weakness of the facial and jaw muscles. Marked gingival hypertrophy developed. At this time (third hospital day), while loss of painful sensation and muscle paralysis was rapidly ascending to the point where intercostal muscles were becoming weak and cyanosis was apparent, he was given 100 mg. of hydrocortisone by intravenous drip during a five-hour period and simultaneously started on therapy with 25 mg. of prednisolone orally four times daily. The patient became less apprehensive and appeared less cyanotic within three hours after corticosteroid therapy was started.

Pinprick sensation was restored over the entire body, and the cranial nerve palsies showed marked improvement during the first 12 hours of corticosteroid therapy. Within two days, the cranial nerves were functioning normally with the exception of the absent gag reflex. At the end of the sixth hospital day, and the third day of treatment with corticosteroids, residual neurological finds were limited to the bladder and rectum and the absence of abdominal and gag reflexes was noted. All motor weakness and sensory loss had disappeared. He was, however, incontinent of feces and still manifested total urinary retention. Genitourinary track infection became manifest at this time, and Escherichia coli were cultured from the urine. Therapy with oxytetracycline was started and prompt improvement occurred. The prednisolone dosage was gradually reduced during the next week, and the patient was given bethanechol (Urecholine) chloride in an attempt to improve bladder tone. Spontaneous micturition was attained, and catheterizations were discontinued. The prednisolone therapy was discontinued after a total of three weeks treatment. Six weeks after onset of the urinary retention, bladder function was normal and recovery was considered complete.

Comment

The neurological complications of antirabies vaccine (rabbit central nervous system preparation) fall into three categories: (1) peripheral neuritis, most commonly of the facial nerve, usually with complete recovery; (2) acute encephalomyelitis with ascending paralysis (Landry's paralysis) with encephalitis; and (3) dorsolumbar myelitis (classified as Landry's paralysis without encephalitic components). Other complications include induration and redness at the site of injection, at times with fever. Blatt and Lepper [5] also report fever with subjective nervous system involvement, generalized weakness, stiff neck, and weakness in the legs but no objective signs of neurological involvement.

In general, patients may develop neurological complications from the time of the 4th to the 14th day of injection. Complications may occasionally develop after the completion of the course of vaccine. The usual vaccination is a 14-day course of virus grown on animal central nervous system, generally rabbit central nervous system, and the virus is either phenol-killed or inactivated. The spinal fluid in the patient shows variable degree of lymphocytosis and elevated protein level. The pathology found in autopsy cases is rather consistently that of a focal demyelinating process involving the cord and the brain. There is often associated perivascular inflammation.[6] Most workers now believe that this is a specific allergic reaction to a tissue specific antigen found in central nervous system.[7]

While it is often erroneous to draw conclusions from a single observed case, the dramatic response of our patient to corticosteroids while he was pursuing a rapid downhill course could lead one to believe that corticosteroids had, at least, resulted in a dramatic improvement, if they had not saved the patient's life.

Blatt and Lepper [5] reported three patients treated with ACTH; two showed dramatic response, and the third was treated somewhat erratically and showed no appreciable benefit. The demyelinating lesion is believed to be that of a specific antibody antigen reaction; therefore, corticosteroids would be expected to be of benefit in blocking this antibody reaction. Corticosteroids have also been shown to lessen inflammatory reaction of the central nervous system to induced irritants, namely iophendylate (Pantopaque).[8]

Summary

A patient with rapidly ascending encephalomyelitis after 12 injections of Semple-type antirabies vaccine (rabbit central nervous system preparation)

apparently responded dramatically to the administration of corticosteroids.

Office of the Surgeon General, Washington 25, D. C. (Major Briggs).

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PENETRATING WOUNDS OF SKULL DUE TO METAL AXLE OF COLLAPSIBLE TOY CARS

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and
John O. Sharrett, M.D., Baltimore

This report pertains to three children whose skulls were penetrated by the metal axle of rubber or plastic toy cars. In each instance the toy car was lying on its side with the metal axle perpendicular to the floor. When the child fell and his head struck the toy, the rubber or plastic chassis of the car held the axle in an upright position so that the metal axle penetrated the skull as the chassis collapsed or crumbled (fig. 1). In two of the three cases, a flange on the axle prevented a penetration of more than a few millimeters through the skull. It is believed that this type of accident would be less likely to occur if toys were made in such a way that the chassis would not crumble or collapse any more readily than the axle or if each wheel were mounted on a small pin rather than an axle traversing the width of the vehicle. It is therefore hoped that the report of these cases will stimulate the reporting of any similar cases so that toy manufacturers may have the benefit of the statistical incidence of this type of accident.

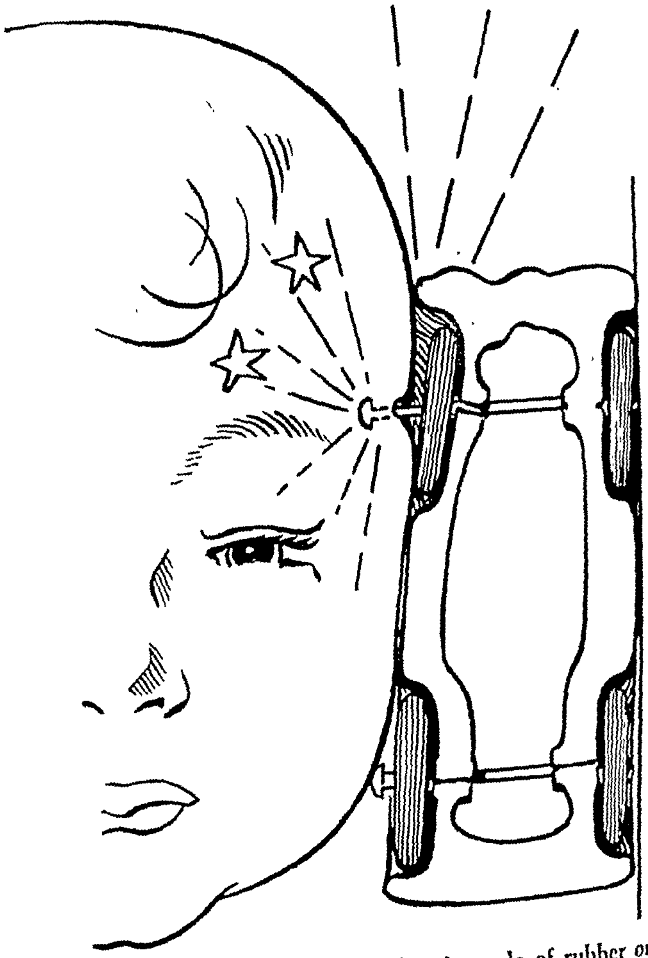

Fig. 1.—How metal axle with chassis made of rubber or plastic enters child's head.

Report of Cases

CASE 1.—A 21-month-old boy, referred by Drs. Theodore Kaiser and William Brendle, was admitted to the Harford Memorial Hospital on May

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14, 1959. He had fallen on a rubber tractor lying on its side, and the metal axle had penetrated his skull just above the right mastoid. Attempts by the family to extract the toy from his head were unsuccessful, so the rubber chassis was cut away from the axle and the boy was brought to the hospital with the tip of the axle imbedded in his skull just above the right mastoid (fig. 2). He was taken to the operating room, where, after he had been put under general anesthesia, a trephine was made just above the foreign body, the bone adjacent to it was moved with a rongeur, and the axle was removed. The dura mater was not perforated. Prophylactic chemotherapy was administered, recovery was uneventful, and neurological examination showed normal results throughout.

Fig. 2 (case 1).—Lateral view (*left*) and anteroposterior view (*right*) of skull, showing metal axle imbedded in skull just above right mastoid.

Case 2.—An 8-month-old boy, referred by Dr. Donald E. Fisher, was admitted to University Hospital on Jan. 29, 1959. He had fallen on a toy tractor, the chassis of which was made of rubber, and the metal axle penetrated his skull in the right side of the occipital region. About 3 mm. of the axle remained impacted in the skull until it was forcibly extracted, after which he was brought to the hospital. Physical examination showed normal results except for a small puncture wound of the right side of the occipital region. Roentgenograms of the skull showed a small puncture wound of the right side of the occipital bone but showed no evidence of depressed fragments of bone. Prophylactic chemotherapy was administered, his hospital course was uneventful, and he was discharged on Feb. 7, 1959. He was last seen on March 2, 1959, at which time he was asymptomatic. Neurological examination showed normal results throughout.

Case 3.—An 11-month-old girl, referred by Dr. Julius Chepko, was admitted to University Hospital on Nov. 26, 1959. She had fallen on a toy truck, the chassis of which was made of plastic, and the metal axle penetrated her skull just posterior to the left side of the mastoid. As the axle penetrated the skull, the wheel on that side was displaced until it came to lie against the other wheel, which was held in place by the flange on the opposite side of the truck. All of the axle but the flange on the opposite side and the width of the two wheels penetrated the skull. After considerable force had been applied, the axle was withdrawn, and only minimal bleeding occurred. Prophylactic chemotherapy was administered, recovery was uneventful, and the child was discharged from the hospital on Dec. 2, 1959. Neurological examination showed normal results throughout.

Comment

The surgical management of these patients requires no further comment. Fortunately each of the three children recovered, and it does not appear that any of them will suffer any permanent disability. If two associates working in the same office have encountered three such cases within one year there must be other clinicians who have had similar experiences.

803 Cathedral St.

SPECIAL CONTRIBUTION

RESEARCH AND TEACHING IN MEDICAL SCHOOLS

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President Eisenhower noted in the statement accompanying his approval of the budget appropriation bill for the Department of Health, Education, and Welfare "his concern for the potential harm in the diversion into research of the manpower and other resources needed for equally vital teaching and medical practice." There is a fundamental error in setting up these separate functions of medical colleges as competitive or mutually exclusive. Surely, the United States has the resources to meet the needs of the full trinity included in the President's message, namely, research, teaching, and medical care.

Not long ago it appeared that our resources were insufficient for research; yet when the need became apparent, the funds were made available. Only 3.5 million dollars was expended for separately budgeted research in medical schools in 1940-1941. For 1957-1958 the amount was 105.5 million. It is significant that this sum is about two and one-half times greater than similar expenditures in 1953-1954 and six times greater than for 1947-1948.

The impact of research on medical education is also indicated by present budgets of medical colleges. Nine representative public and seven private medical schools spent a total of $11,300,000 for research in 1948, with an increase to $31,300,000 in 1958.[2] Such increases overshadow the limit increments for teaching. Recently the opinion was presented[3] that this explosive expansion of research is having an adverse effect on teaching in institutions of higher learning in the United States, and significantly the author preferred to remain anonymous. Snoke[4] also raised the question of an "overemphasis on research" in the modern medical school. Barzun[5] stressed the effect of the present attitude of "inherent sanctity" and "deemed superiority of research over teaching."

Need for Positive Viewpoint

These negative viewpoints neither come to grips with the basic issues nor help resolve the problem. The answer does not lie in degrading our medical colleges to vocational schools by having them forego research, nor is the remedy to be found in transforming medical schools into research institutes only, by their abandonment of teaching and the training of physicians. The solution does not lie in curtailing research, but rather in simultaneously bolstering the teaching effort with similar support.

Research and teaching are inseparable;[5] they complement each other. The university is the site of scholarship, and research is its catalyst, particularly at the graduate level of medical education. Any department or faculty lacking a dynamic research program is static, sterile, and doomed to mediocrity. Research is obligatory for the medical school to meet its responsibility to advance medicine. Research attracts capable persons to teaching and can make a good teacher a better one.

Strengthening research does not, however, require that teaching be down-graded; our failure to champion teaching is the source of our difficulty and is short-sighted. Each can make its own contribution and both should be promoted in relation to the whole problem of medical education and its over-all needs. If the good teacher's talents and abilities lie in the transmission of knowledge and the stimulation of students, he should not also be compelled to "produce or perish" and to vie with his research colleagues in the acquisition of grants and in research publication. His contribution lies in bringing the benefits of research into the realm of pragmatic reality for the practitioner and the patient, and it should be evaluated for its own true worth and receive its due recognition.

Education in medicine, like all teaching, is best achieved by providing the avid pupil with a scholarly atmosphere and, above all, with capable and inspiring instruction. Without good teaching, scientific research itself will ultimately be curtailed because of insufficiently and inadequately trained candidates. What is needed is the maintenance of a proper balance between research and teaching, with full support of both. The growing shortage of physicians accentuates the need for good teaching in medical schools. A recent editorial by Dock[6] deals with the question "Should teachers all be investigators?"

Research and the Student

The medical college certainly has the obligation to seek the student who shows promise as a research worker and to offer him every encouragement to choose an academic career. Only a few students in any class will be found capable of embarking on a career of investigation. Working with a good research worker can identify a student with

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research permanently; yet stimulating teaching can give more pupils the proper background and the fundamental motivation to choose such careers.

Most medical students will become practicing physicians. Research experience alone cannot prepare a physician for the practice of medicine. The student must organize a large body of theoretical and factual knowledge in a relatively short time and learn to apply it to the individual patient, a test for good pedagogy if there ever was one. Much of the subject matter and art of medicine can be taught best by precept and example; this clinical experience requires stimulating teaching.

Support of Research Alone Harms Both Research and Teaching

In the past the research worker was condescendingly considered an impractical maverick, receiving scant support and little recognition. This has all changed now, for today research has both prestige and the material benefits of control of funds, equipment, technicians, travel allowances, fellowships, prizes, and awards, and preference in promotions in the academic hierarchy.[6] Hence, it follows that many teachers in medical colleges now make research their primary interest; they view teaching as a chore often in conflict with their research effort and, quite understandably, reduce their teaching to the absolute minimum. Medical colleges also promote this policy because of their emphasis on publication for the reputation of the institution.

The danger is that nonresearch functions may be affected unfavorably. Snoke[4] indicated the detrimental effect of the unbalanced emphasis on scientific investigation on individual patient care and questioned "whether medical care is as superlative in university teaching hospitals as we would expect in this 'best of medical worlds,'" and noted the further consequence of the "blind spot in our thinking due to a refusal or inability to accept responsibility for complete education of the physician." Some research workers contribute to the difficulty by disparaging the contribution of the teacher. This belittling in the "teacher's own bailiwick" diminishes the appeal of teaching and contributes to the prevailing feeling of neglect and frustration on the part of the gifted teacher in medicine.

An imbalance appears because of the present deemphasis of teaching and its lack of financial and other support. This has resulted in a growing dichotomy in our medical colleges, best seen in a department such as pathology. Here members of the staff are subdivided into those responsible for routine services to the patient, teaching, and resident training on the one hand; and those carrying on research, often exclusively, on the other. This separation does harm to the student, the instructor, the department, the college, and the specialty. It serves to isolate research from routine performance in pathology, diminishing rather than increasing the research potential of the specialty as a whole.

The largest number of vacancies in medical colleges today exists in pathology, and vacancies are being filled by research workers who are untrained and unqualified in pathology. The premise is that such candidates will not be distracted by the obligations of teaching and diagnosis, and that better use will therefore be made of grant support for larger, more creative and productive research programs. This trend in pathology can be harmful to the specialty in particular, and to medical education in general. This policy bodes ill for the quality of the future instruction in pathology and for the stimulation of students to choose pathology as a career to meet the serious shortage in this specialty. Promoting only research in pathology will not achieve this objective. The solution lies in developing a program of training for mature, capable pathologists who will be good teachers of pathology and will also be qualified to do creative research in morphology, a field of increasing promise.

Research workers in pathology have the usual commendable compulsive, instinctive, tenacious drive to probe for the truth in the spirit of true scholarship. Equivalent commendable idealism and scholarship exist in the daily stint and instruction in the autopsy room. The autopsy lacks the aura of experimental research and its findings have less certainty of productive publication. Yet, as a teaching instrument and a means of integration and correlation, so pressing a need in medical education today, the autopsy is incomparable.[7] In the present atmosphere emphasizing laboratory research on "four-legged animals," the autopsy is being neglected. This discounting of the autopsy in medical education[8] is new and is only a specific manifestation of the changing over-all attitude toward teaching in our medical colleges. The decline of interest in the autopsy follows from the replacement of the patient as the teaching instrument by the blackboard, the chart, the laboratory, and the conference. Cannon[9] and others[10] have eloquently refuted this attitude toward the autopsy.

A change from this negative attitude toward teaching to one of more healthful emphasis on good instruction in our medical schools can well be initiated by better "hard" budgetary and grant support of the autopsy.[11] Adequate financial support is now more imperative than ever because of the ever-increasing complexity of complete investigation of the dead human body, in the face of the effectiveness of modern therapy, and the growing importance of biochemical mechanisms and viral infections. One can hardly visualize the training of the practicing physician without adequate analytic presentation of the autopsy. The "grand human experiment" should be exploited to the full for the part it can play for the student and the staff physician in their comprehension of disease in the individual patient.

Balanced Emphasis on Teaching Essential

Better support of teaching in our medical schools is overdue; there are too few grants for the improvement of teaching. Grant agencies often specifically eliminate or limit permissible time for teaching. Training grants are often limited to research training. If grant funds were available to support teaching in medical schools, and experiments in pedagogy also were supported, some of the unwarranted conflict and unneccessary rivalry between research and teaching would be eliminated and teachers would be encouraged to strive for greater achievement.

There are not too many rewards for experimental research, but rather too few for teaching performance. Awards for a contribution to teaching, such as the Lederle Faculty Award, can be of assistance. Salaries should be made attractive to increase the number of candidates for both teaching and research, so that our too few teachers will not be overburdened without time for creditable research. Subsidization of teaching and the training of teachers is imperative if the projected creation of additional medical colleges [12] is to be at all possible. A serious shortage of teachers already exists in the field of medicine. Such support can expand total research and further extend its remarkable benefits to the whole faculty and student body.

Grants should be available for experimentation in pedagogy to seek more efficient means of transmitting information and making learning more effective. Audiovisual aids should be adapted and exploited and every means of dramatic teaching and demonstration introduced. The use of television in intramural programs should be supported. The development of a library of film strips, motion pictures, tape and kinescope recordings of lectures and classic experiments and techniques, and animated films for instruction in the use of modern complex instruments are resources to be developed. The recording of outstanding lectures, such as those of the Harvey Society and Sigma Xi, for use in outlying medical schools is worthy of trial. Support for exchange and visiting lecturers for undergraduates and residents should be available. The development of carefully compiled subject curriculums such as those now coming into existence under the auspices of the National Science Foundation in the Biological Sciences Curriculum Study, is a promising venture for medical education. The proper selection and accentuation of general principles is imperative, if the student is not to be overwhelmed by unorganized detail in a rapidly expanding field; this requires careful over-all evaluation of subject matter and meticulous weighing by experts. Development of meaningful tests to determine mastery of a subject is needed as a means of objective evaluation of pedagogic methods. Technicians, clerks, and equipment can be helpful in teaching too. Support is desirable for the wider use of small groups in instruction and seminar sessions. Means of minimizing the harmful effects of unnecessary competition, with its undue stress among the student body, must be sought. Better understanding as well as mere learning must be promoted. These are challenges, not mere platitudes, and offer us worthy objectives which better teaching can help to achieve.

Summary and Conclusions

An appeal is made for a proper balance in medical education, with appropriate stress on research and due emphasis on the important function of teaching and training physicians. Teaching can be as vital and rewarding as research. There must be a proper synthesis and mixture of the functions of teaching, research, and care of the patient; these should be complementary, not competitive. A proper mixture of all three functions yields a potent "clear solution," if due recognition is given to each function with an understanding acceptance of the necessity, significance, and contribution that each provides in a medical school. Virchow's statement applies to the modern medical school, "as big enough to accommodate all parties, if they do not want to be exclusive, if they do not aim to extend beyond their boundaries, if they do not pretend to achieve everything." [13] Let us restore the proper balance in our medical schools by doing for teaching what we have done so well for research, and medical education will be revitalized.

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CLINICAL SCIENCE

CLINICAL AND EXPERIMENTAL NEPHROPATHY RESULTING FROM USE OF NEOMYCIN SULFATE

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and
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Prolonged parenteral therapy with neomycin sulfate may be accompanied by renal lesions.[1] We have studied, by stain and microscopy procedures, lesions ascribed to neomycin which were experimentally induced in the kidneys of rabbits, and we have compared them to lesions found in human autopsy specimens.

Experimental Studies

Five rabbits (average weight 1.7 kg. [4 lb.]) were injected with 35 mg. of neomycin daily in the marginal ear vein. After 30 consecutive days of injections the rabbits were killed, and sections of kidney tissue were immediately fixed in formaldehyde and studied by staining procedures described in the standard textbooks[2]; minor variations are indicated.

Human renal tissues were obtained fresh at autopsy from three patients who had received large amounts of neomycin during the terminal stages of their diseases. These tissues were treated identically to the rabbit specimens. The lipid components of the lesions[1] were studied with use of Oil red O, Nile blue sulfate, and Sudan black B. Amyloid was stained by the Congo red amyloid stain. Potassium was demonstrated by MacCallum's method as modified by Gomori.[2a]

No deaths, episodes of diarrhea, or other grossly apparent untoward reactions were noted in the control or experimental rabbits. In all experimental animals, renal vacuolization was found; the control group displayed no nephropathy.

The typical experimental renal lesions consisted of focal areas of foamy vacuolization of the epithelial lining of the convoluted tubules. This change was most marked in the proximal segments and was seemingly absent from the loops of Henle. The glomeruli remained unaffected (fig. 1), and there was distinct focal vacuolization of the proximal tubular epithelium. The vacuoles were ill defined and clear and replaced the cytoplasm (fig. 2); concurrently nuclear displacement occurred. Although the changes were not generalized throughout the sections, they were quite definite in certain areas (fig. 1*A* and *B*). The majority of the nuclei show pyknosis and karyolysis and, in some areas, frank tubular necrosis. Other distinctive features noted were granular necrosis (fig. 1*C*) and poorly outlined, debris-laden tubules. Staining characteristics of the sections revealed no evidence of lipids, potassium, or amyloid in the vacuoles.

Human renal lesions appeared to be morphologically identical with those presented by other investigators,[1a] and the staining procedures were identical to those used on the experimental rabbit lesions.

Report of Cases

Case 1.—A 52-year-old man was admitted to Parkland Memorial Hospital in a clinical state of severe septicemia. The patient received massive intravenous administration of neomycin during the next few days. The amount was in excess of 16 Gm. The patient pursued a fulminating downward course and died. Microscopic sections revealed a renal lesion which showed tubular degeneration with striking vacuolization of the lining epithelium.

Case 2.—A 79-year-old man was admitted to the hospital with the diagnosis of chronic bronchopulmonary disease of several years' duration and emphysema with fibrosis. He also had a history of hypertension and kidney disease. Blood pressure at the time of admission was 110/30 mm. Hg. Four days prior to admission and during his hospital stay the patient had diarrhea; the stools were green and watery but not bloody. Although he had severe diarrhea the potassium level was maintained within the normal limits. Irrigation with 250 cc. of neomycin was performed several times. In addition, 30 Gm. of neomycin was given orally and intravenously. At autopsy massive bronchopneumonia with abscess formation was noted. The kidneys showed benign arteriolar nephrosclerosis and massive degeneration of the proximal tubules with striking vacuolization.

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Case 3.—A 30-year-old woman was admitted to the hospital after she had given birth to a normal child at home. At the time of admission the diagnosis of severe bronchopneumonia with bronchopleural fistula was made. Neomycin was given intravenously in the dosage of about 16 Gm. for eight days. At autopsy the diagnosis was confirmed; however, there was striking acute tubular nephrop-

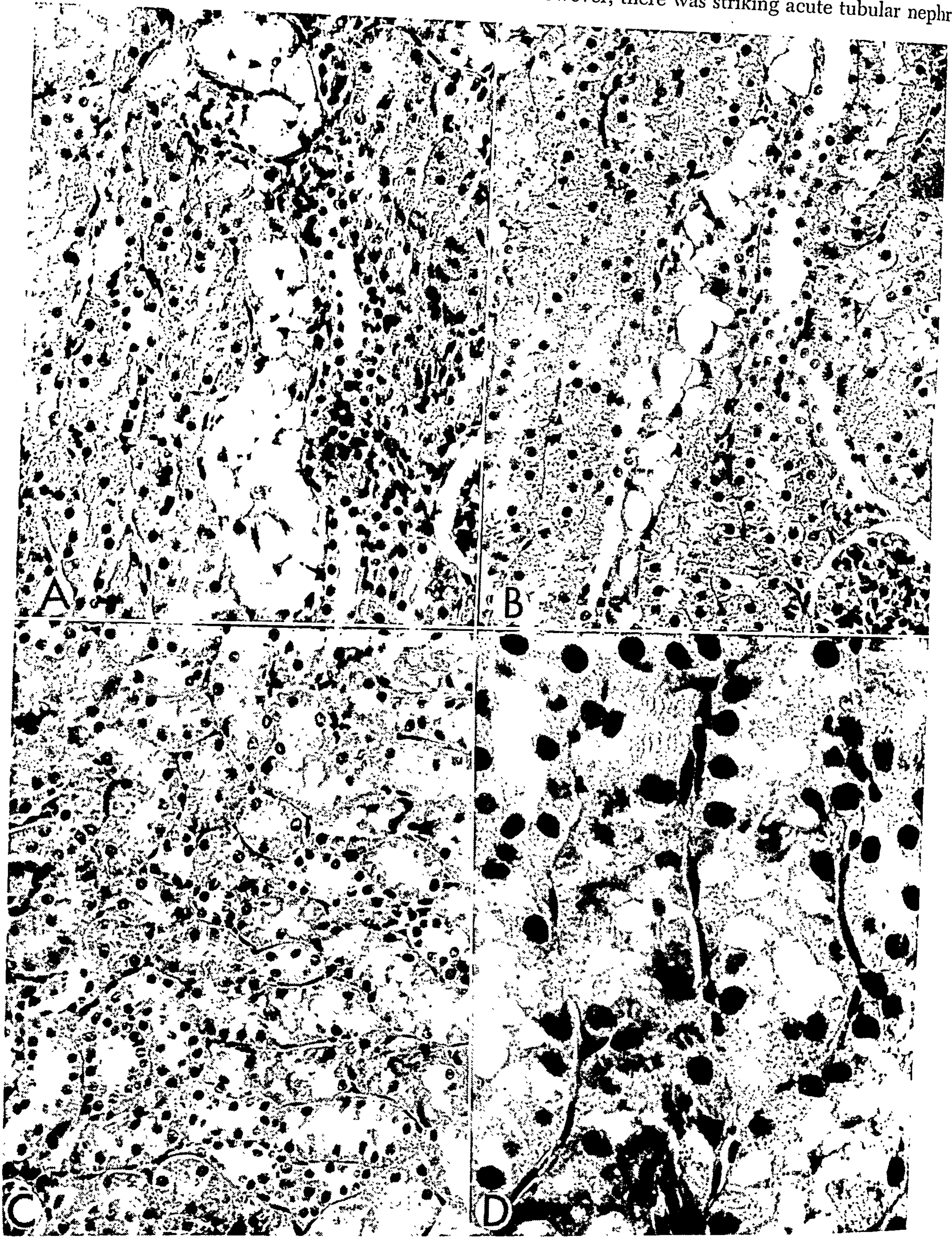

Fig. 1.—*A*, vacuolar degeneration of tubules. *B*, distinct vacuole of tubules. *C*, degeneration of cytoplasm. *D*, granula degeneration of cytoplasm.

athy characterized by the marked vacuolization of the proximal convoluted tubules.

Comment

This study has been concerned with the nature of the vacuoles found in the epithelial lining of the renal tubule associated with neomycin therapy.

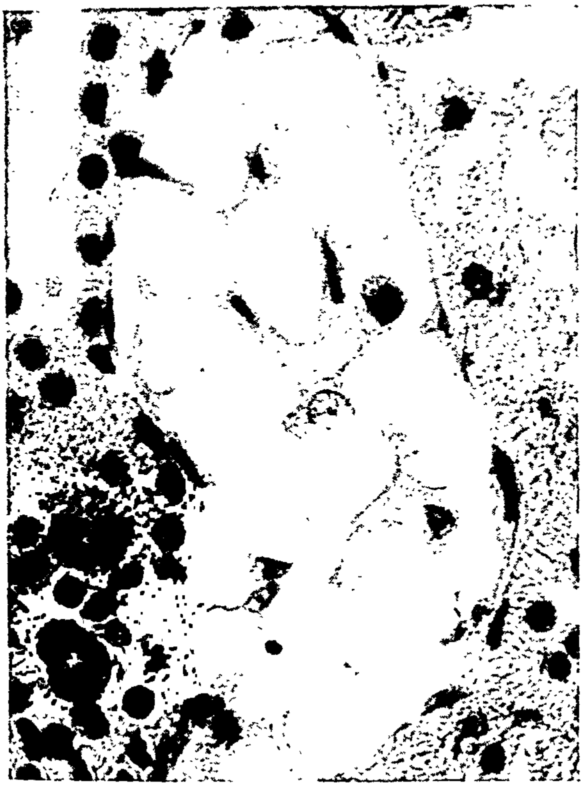

Fig. 2.—Vacuolar degeneration of tubules.

Three points have been covered by this study. 1. Neomycin alone causes a specific renal lesion in the healthy animal. 2. Staining procedures reveal that the experimental rabbit lesion and the human lesion react similarly. 3. The exact nature of the vacuoles is as yet unknown, as staining procedures failed to yield evidence of their composition.

Studies of other possible causes of similar pathological renal changes indicated that the experimental rabbit lesions were produced in the absence of any detectable causes of nephropathy except the neomycin.

Although there was a possibility that more subtle systemic imbalances existed than are usually appreciated by routine procedures, the simplicity of the experiment and the ease in reproducing results lead us to believe that neomycin does cause nephropathy.

As the experimental lesions had the same staining characteristics and morphologic appearances as did sections made from tissues of the patients who had fatal cases of nephropathy, it was concluded that these lesions were essentially the same histochemically, morphologically, and, presumably, clinically.

Summary

Neomycin sulfate per se acts as a nephrotoxic agent with specificity for the renal tubules. Concomitant acute or chronic infections or other types of systemic degeneration apparently are not major agents in the production of the renal damage. The exact nature of the content of the ballooned cytoplasm remains unknown, although it is not fat, amyloid, or potassium.

The neomycin sulfate used in this study was supplied as Mycifradin sulfate by the Upjohn Company, Kalamazoo, Mich.

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TRUE GENIUS.—The person of true genius is a *persona sui generis;* he possesses certain qualities not to be found in the ordinary human being—above all others two which may be accounted as essential and distinguishing characteristics, namely originality and creative imagination. To these we must add (1) an irresistible urge to fulfill what he conceives to be his ordained mission in life, (2) the possession in an extraordinary degree of the faculty of intuitive perception and (3) unconventionality in thought and actions. *Inward Urge.*—The typical genius is a person clearly distinguished by a singleness of purpose and a self-conviction of his own rightness, and he feels himself to be under the sway of a constant inward urge to pursue his destined course and to express and assert himself. No goal is too distant to be reached, no obstacle too great to be overcome.—W. A. Wells, A Doctor's Life of John Keats, Vantage Press, New York, 1959, page 224.

THE JOURNAL
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THROMBOTIC THROMBOCYTOPENIC PURPURA

AN infrequently diagnosed disease of unknown cause, thrombotic thrombocytopenic purpura, has constituted a medical enigma. Described by Moschcowitz in 1925 and first diagnosed ante mortem in 1952, this condition is characterized by hemolytic anemia, severe thrombocytopenic purpura, and small vessel thrombosis. Clinically, the extreme pallor and a spectrum of neurological and mental changes, varying from day to day or progressing to coma, distinguish this type of case from thrombocytopenic purpura. The typical histological lesion of the disease has been clearly described and is easily recognized when found. The predilection for internal organs such as brain, heart, pancreas, and adrenals may render biopsy diagnosis difficult. Recognition of the fulminant type is a problem only because of its rarity; however, an increasing number of reports during the last three years has extended the concept of thrombotic thrombocytopenic purpura to milder, more chronic cases as well as to wider clinical variants. Improved recognition based on greater familiarity and a higher index of suspicion will probably reveal a greater incidence of this disease.

The etiology and pathogenesis remain obscure. A triple autoimmune reaction, a vascular hypergic response to antigenic stimuli, or a collagen disease has each been postulated in turn. Even the nature of the hyaline material that makes up the vascular occlusion has not been determined, although histochemical studies have been made. Possibly electron microscopy of suitable biopsy material might show an ultrastructure sufficiently characteristic to reveal the nature of the hyaline material of the lesion. It is hoped that such electron studies will be made when the opportunity presents itself in order to increase our understanding of this disease.

Treatment, especially in fulminant cases, has given discouraging results up to the present, with the disease generally considered fatal. Whether this is due to failure of early recognition, the difficulty of obtaining a suitable biopsy specimen, or the lack of sufficiently aggressive therapy is not clear. During the last few years, however, fairly prolonged remissions have been reported. Furthermore, as described in this issue of THE JOURNAL (page 778), survival without relapse for longer than eight years seems to indicate that a cure may be possible. From this experience, massive steroid therapy followed by splenectomy has been the recommended therapy.

THE LITTLE WORLD OF THE BIG GLOBULINS

The terms associated with the macroglobulins have been introduced only recently into medica literature. They are as enchanting and the origi as elusive as the leprechauns, the banshees, and th gremlins. A comprehensive review of the macroglobulins, prepared by Ritzmann and associate from Galveston and published in the current issu of the *Archives of Internal Medicine*,[1] discusse cryoglobulins, macrocryoglobulins, cryogelglobulins, macrocryogelglobulins, paramacroglobulins glycolipoproteins, paramyloidosis, immunoelectrophoresis, uroparaproteins, fibrinasthenia, properdi activity, ergastoplasm, paraproteins, and com paraproteinemicum. Macroglobulinemia is associated, above anyone else, with Waldenström, clinician investigator from Sweden, whose firs contribution to this subject was published in 1944, only a few years after he had finished his forma scientific education.

Macroglobulins are not always foreign substances. They have been identified as norma constituents of human blood serum. They constitut less than 5% of the total proteins in the normal. I association with neoplastic diseases, particularl lymphoma, multiple myeloma, cancer of the uteru and bronchi, they may comprise 15% of the tota proteins. A number of other dyscrasias revea macroglobulins in concentrations of this magnitud Included in this category are the connective tissu disorders such as polyarteritis, systemic lupu erythematosus, rheumatoid arthritis, Felty's syndrome and Sjögren's syndrome; kala-azar, toxoplasmosis, congenital syphilis and chronic hepatitis, as well as the nephrotic syndrome, amyloidosis, and cirrhosis of the liver. These maladies ma be associated with *secondary* macroglobulinemia Primary macroglobulinemia should be reserved fo the eponymic term. The concentration of the larg molecules is usually greater than 15%. The molecular weight of normal serum globulin is approx mately 160,000. The molecular weight of Bence Jones protein is 35,000 and that of the macroglobulins may be as high as 1,800,000. The macroglobulins probably are the result of aggregations or polymers of the globulins of normal molecular weight.

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There are several clinical features always or usually identified with the primary syndrome, macroglobulinemia Waldenström. Paraproteinuria, sometimes of the Bence Jones type, may be demonstrated in selected patients. Whether these uroparaproteins are synthesized independently from the macroglobulin, as are the Bence Jones proteins in multiple myeloma, has not been established. Cold intolerance with clinical features of Raynaud's syndrome may be distressing. The patients respond poorly to infection because of a deficiency of antibodies. The hemorrhagic tendency is frequently apparent. The patient may suffer spontaneous bleeding of the mucous membranes of the mouth during sleep. Hepatomegaly and splenomegaly are significant findings upon physical examination. Bone pain is not a common feature. Diffuse osteoporosis, rather than punched out lesions roentgenographically as observed in multiple myeloma, has been noted. Amyloid deposits have been identified in various structures of the body. A positive Congo red test may be a false positive laboratory finding. Inhibition of pseudopod formation of the platelets may be demonstrated by electron microscopy.

A number of laboratory tests are helpful in screening or in confirming the diagnosis. A marked rouleau of the red blood cells is found in macroglobulinemia as it is in multiple myeloma. The modified Sia test is not difficult to perform, and information gained from this may be helpful. The sedimentation rate is probably the most important screening test. Usually there is a marked acceleration of the rate. Determination of this activity at different temperature ranges (thermosedimentation rate) may provide critical information regarding the character and type of paraproteinemia. The determination of the serum viscosity at different temperature ranges and the reduced specific viscosity are further refinements of Waldenström's Serum Viscosity Index. Paper electrophoresis and ultracentrifuge measurement are refinements of laboratory diagnostic procedures that leave no doubt regarding the validity of the diagnosis. The bone marrow should be revealing in multiple myeloma. In macroglobulinemia the identification of lymphoid or lymphoreticular cells is helpful. Immunologic studies with rabbit or horse antimacroglobulin serum provide help in distinguishing between the primary and secondary forms. The secondary macroglobulinemia does not react immunologically as does the primary form.

The source of the macroglobulins in health and in sickness is believed to be the lymphoid-reticular cell, similar to the plasma-myeloma cell of multiple myeloma, which is responsible for the abnormal globulins and possibly the Bence Jones proteins in the urine in this malady. In primary macroglobulinemia, an intrinsic, malignant, irreversible alteration of the reticuloendothelial system, possibly associated with an enzyme defect in the process of protein synthesis, is responsible. Secondary macroglobulinemia is associated with the response of the reticuloendothelial system to an extrinsic, benign, and reversible stimulus. The natural history of primary macroglobulinemia is not extended. Death may intervene in the malignant type within a few weeks. A survival of two or three years may be anticipated in the less malignant type. Death is usually due to an overwhelming infection, severe anemia, hemorrhagic diathesis, complications due to environmental cold sensitivity, or coma paraproteinemicum.

The steroids have been of some value in treatment. Other general measures include periodic transfusions and antibiotics when indicated. Patients suffering from macrocryogelglobulinemia or macrocryoglobulinemia, particularly those with a high temperature amplitude, benefit by a high constant environmental temperature. One patient has been described in the literature who remained symptom free and relatively well with an environmental temperature of 80° F. Local and general symptoms appeared with the fall in environmental temperature.[3] The value of the mercaptans as a therapeutic agent in breaking down the large molecules is being investigated. Further information on the macroglobulins may reveal a battery of clinical entities, rare to be sure, but extremely interesting in chemical and enzymatic pathogenesis.

RETINAL DETACHMENT

Although the ophthalmologist plays the leading role in the treatment of retinal detachment, the family physician may have to make important decisions. He may have to decide whether an elderly patient can endure long general anesthesia and confinement to bed with a minimum of movement. He may have to evaluate the emotional reserve in a patient already apprehensive and depressed by sudden blindness. He may have to participate in long-term postoperative care. He will be better able to cooperate if he has a general idea of the complex problems involved. Robert Fink's[1] recent explanation provides a brief synopsis of the pathogenesis and current treatment. About 50% of all detachments occur in nearsighted people; another 20% develop within three years after cataract extraction, not as a result of poor surgical technique or complications but because the changes in the lens are part of a dystrophic eye condition. Clinically, 10% of detachments result from trauma. Although children who have congenital retinal weakness may be victims, detachments occur usually in the 50-to-60-year age group.

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[1] Fink, R.: Retinal Detachment, Journal Lancet 80:180-183 (April) 1960.

An important etiological factor is the vitreous which fills the cavity of the eye. The vitreous, a viscous fluid, contains collagen fibrils which are attached to the retina. Pathological changes in the vitreous, which may develop for various reasons, cause it to shrink in size, and its elastic collagen fibrils then put tension on the delicate sensory portion of the retina. Thus, tears may occur in spots that have been weakened by inflammation, trauma, or other causes. Serous fluid seeps through the holes, and the normal movements of the eye force the fluid behind the retina, ballooning it forward.

This tugging on the retina by the shrunken vitreous brings on the patient's initial complaint, that of flashing lights. Next he may observe floating black specks caused by small clumps of blood in the vitreous. Shortly, he may notice a "curtain" across his vision, which indicates that the retina has detached. The patient should be put to bed to see if the fluid beneath the retina will be absorbed and to permit the retina to settle back against the choroid. If the detachment is relatively small, with no evidence of vitreous traction, and if the retina settles back during bed rest, diathermy alone may be sufficient treatment.

The ophthalmologist must search for all tears in the retina and seal them off. However, if there is evidence of a strong vitreous pull, diathermy alone will not suffice, and more complex surgery such as scleral resection, a scleral-buckling operation, or a vitreous implant may be considered. The later methods of handling the more severe detachments are said to have increased the chance of success, but nearly one-fourth of all operations for detachment still end in failure.

The postoperative period is trying for the specialist and the patient. Intraocular hemorrhage, infection, and further retinal shrinking sometimes occur. The family physician too must be on the alert for possible systemic complications.

POSITIVE TOXICOLOGY

Among the many striking presentations at the recent annual meeting, in Chicago, of the Federation of American Societies for Experimental Biology, was the program on Problems in Toxicology. A series of papers delivered under the chairmanship of Drs. Chauncey D. Leake and W. Henry Sebrell Jr., described the "man-made noxious environment" that is developing about us. It is creating medical problems faster than they can be solved. New unknowns rear their heads each day, in the foods and cleaners used in the home, the drugs and cosmetics sold in stores, the raw materials and new products in industry, the fertilizers and pesticides in agriculture. Since the discovery of ionizing radiations just before the beginning of this century a whole new category of viciously destructive radioactive materials has complicated the picture. In addition, the recent development of submarine and space travel confronts future travelers with the possibility of confinement within small capsules, cells, or coops in particularly close and inescapable contact with new chemicals. The monoethanolamine problem recently described by Ebersole[1] is but one instance.

Notable for constructive thinking in this program was the contribution by H. F. Smyth Jr. on th desirability of recognizing toxicology as a scientifi discipline. It was pointed out that the toxicolog of the past has been essentially negative or destruc tive. Poisons were used to kill people or animals. A toxicologist was one who could analyze gastri contents for arsenic and in general was concerned with the detection or prevention of crime.

That this narrow concept of toxicology is anti quated follows from the realization that all poison are simply excesses. Nearly every known substanc is tolerable, useful, or even necessary in som limited amount and injurious in larger amounts The recent association of oxygen with retrolenta fibroplasia is an important illustration; it show how a substance on which our lives depend from one moment to the next became, when misused in ignorance of its dangers, for a time "first among the causes of blindness in children in the United States."[2] An equally striking illustration is the misuse of sodium chloride for packing the vagina post partum; this cruel custom, existing in parts of the Near East, was discovered recently to be the cause of a series of cases of obliterative vaginitis.[3] Similar facts about water intoxication and nitrogen narcosis are now well known and further illustrate that an excess of any substance whatever, no matter how familiar and inert, can be deadly. Thus the toxicology of the future, it was pointed out by Smyth, must be quantitative. Its essence will be the systematic collection of facts about minimum requirements on the one hand and maximum tolerances on the other.

The negative attitudes of the past were expressed in the question, "What will kill?" The positive attitude for the future must be, "What is safe?" The positive toxicology of the future will be concerned with the problems of producing, handling, storing, using, or discarding safely the innumerable dangerous substances that we are learning to live with. Mankind has learned to handle with apparent impunity such treacherous things as illuminating gas, sulfuric acid, liquid fluorine, and plutonium; it still needs to learn how to handle ethyl alcohol, gasoline, tranquilizers, hormones, antibiotics, and hundreds of thousands of other substances. In a few instances the solution of the problem may lie in legislation, but in most the solution depends on education, which can only be based on painstakingly assembled facts.

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[1] Ebersole, J. H.: New Dimensions of Submarine Medicine, New England J. Med. 262:599-610 (March 24) 1960.

[2] Lanman, J. T.; Guy, L. P.; and Dancis, J.: Retrolental Fibroplasia and Oxygen Therapy, J. A. M. A. 155:223-226 (May 15) 1954.

[3] Frith, K.: Vaginal Atresia of Arabia, J. Obst. & Gynaec. Brit. Emp. 67:82-85 (Feb.) 1960.

[4] Committee on Threshold Limits: Threshold Limit Values for 1959, Adopted at 21st Annual Meeting of American Conference of Governmental Industrial Hygienists, Chicago, April 25-28, 1959, Arch. Indust. Health 20:266-270 (Sept.) 1959.

It was pointed out that a considerable body of such facts already exists. Much has been contributed by pharmacologists, much by industrial hygienists[4]; much comes from other varied sources. The field of toxicology has not yet been unified, and most toxicological research is carried on by workers in contiguous fields. Everyone is ultimately involved, because everyone is working in an increasingly artificial environment. The worship of the "natural" is based on an illusion that can no longer be nursed on a crowded globe; we are sealing our windows against the "natural" outside air, and we no longer depend on the inconstant "natural" light from the sun. In an environment which is so rapidly drifting toward complete artificiality, the accumulating data of the toxicologist become increasing valuable, and it is up to him to interpret them to society.

The training of toxicologists who will measure up to such responsibilities is an important problem, which was discussed by Harold C. Hodge in concluding the program. Clearly, a toxicologist today must be more than a special kind of analytic chemist. He needs a broadly based preparation, but he must assimilate the fundamentals of physics, chemistry, biology, and medicine, with his particular interests in mind. New facts emerge daily to corroborate the assertion that 80% of the poisoning in the United States today goes undetected. The *toxicologist* of the future, carrying on a positive program of laboratory research and public education, will surely make a vital contribution to *preventive medicine.*

THE ANAGLYPHS AND ARTIFACTS OF ASKLEPIOS

An editorial on Asklepios, (L., Aesculapius) was published in this Journal several months ago. Cognizance was taken of the Asklepieion at Epidauros and on the Island of Cos. No attempt was made to recount other extant evidences that honored the great healer, who, in folklore and mythology, preceded Hippocrates. Data to fill this void have been provided by the appearance in English of a volume prepared by Kerényi.[1] The monograph, with an abundance of illustrations, was published originally in Germany under the sponsorship of Ciba, Ltd. The author was formerly a professor of classics and the history of ancient religion at the University of Szeged and of Pécs in Hungary.

The several coins, statues, votive offerings, bas-reliefs, and other material evidences are impressive. There are four votive reliefs on display in the National Museum in Athens. One represents Asklepios accompanied by two goddesses, dated about 390 B. C. One from Thyrea in Argolis depicts the family of Asklepios, c. 370-360 B. C. The third is from the Asklepieion of the Acropolis in Athens. The patient is depicted in the act of receiving medicine from Asklepios; the snake staff is between the patient and physician. The fourth is from the shrine at Epidauros, c. 360 B. C., and represents Asklepios and his two sons, Machaon and Podaleirios, physician and surgeon, respectively. A silver coin from Epidauros, c. 350 B. C., bears an effigy of the great physician. A dog lies under the throne. In Asia Minor a coin, c. 220 A. D., was discovered portraying Asklepios riding on a snake. This is the reverse of a medallion of Alexander Severus from Nikaia, near Pergamon. Also, a medal of Commodus, 180-192 A. D., portrays a ritual statue at Pergamon on the reverse. A marble head of Asklepios, c. 340 B. C., was discovered in a cave on the Island of Melos. The head is now reposing in London in the British Museum. The features peculiar to the "ideal type" of Asklepios have been described by Kerényi as "The eyes seem 'to look upwards and into the distance without definite aim. This combined with the vivid movement gives us an impression of a greater inner emotion, one might almost say of suffering. This god does not stand before us in Olympian calm: he is assailed as it were by the sufferings of men, which it is his vocation to assuage'."

The Asklepieion at Cos was not rediscovered until 1902. Excavations of the temple are far from completed. Something has been known of this sanctuary and the works of art it contained ever since 1891, at which time the Mimiamboi (mimes in choliambic verse) by the poet Herondas, 250 B. C., were published. Herondas described "Women offering sacrifices in the temple of Asklepios" (at Cos).

And on to Rome—a bust of Asklepios remains on the wall that surrounds an island in the Tiber, near the Church of San Bartholomeo, amid several hospital buildings. A snake and staff is also visible, carved on travertine, near the bust. On the Pincian Hill in Rome, an enthroned Asklepios dates from the second century A. D. In the Capitoline Museum a bronze of Asklepios, c. 150 A. D., was recovered from the port of Anzio, the port of entry where Asklepios presumably first set foot on the Roman heartland. The Baths of Caracalla gave up a head of Asklepios, late second century A. D., which is now in the National Museum in Rome.

The several items enumerated do not comprise the entire list of objects of Asklepios recounted by Kerényi. They may be sufficient, however, to provide physicians interested in direct inspection of such items an incentive to visit the museums in London, Rome, and Athens where these representative objects of art are preserved for posterity.

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[1] Kerényi, C.: Asklepios:Archetypal Image of the Physician's Existence, translated by R. Manheim, vol. 3, New York, Pantheon Books Inc., 1959.

including Medicare, and a workroom. The second floor is designed to accommodate conferences, large meetings, and the Woman's Auxiliary.

MASSACHUSETTS

State Medical Election.—Dr. Carl Bearse, of Boston, became the 79th president of the Massachusetts Medical Society at the society's annual council meeting May 16. He succeeds Dr. Lawrence R. Dame, of Greenfield. Dr. David W. Wallwork, of North Andover, was named president-elect. Other officers elected include Dr. William W. Babson, Gloucester, vice-president; Dr. Robert W. Buck, Waban, secretary; Dr. Eliot Hubbard Jr., Cambridge, treasurer; Dr. Norman A. Welch, West Roxbury, assistant treasurer; and Dr. Alfred L. Frechette, Brookline, orator.

Faculty Retirements.—Two members of the faculty of public health at Harvard, Dr. Martha May Eliot and Prof. Bertha Shapley Burke, will retire on July 1. Dr. Eliot will become professor of maternal and child health, emerita, and Mrs. Burke will become professor of maternal and child nutrition, emerita. Dr. Eliot and Prof. Burke become the third and fourth women to be so honored by the university. Helen Maude Cam, is Samuel Zemurray Jr. and Doris Zemurray Stone–Radcliffe Professor of History, emerita, and Dr. Alice Hamilton is assistant professor of internal medicine, emerita. Dr. Eliot also is retiring as head of the department of maternal and child health. She will be succeeded in the latter post by Dr. William M. Schmidt.

MICHIGAN

High Incidence of Hepatitis.—The Michigan Department of Health reported that infectious hepatitis appears well on its way toward setting a record high number of cases in Michigan and the nation this year. Dr. Frederick S. Leeder, Lansing, director, division of disease control, records and statistics, Michigan Department of Health, said that through the week ending May 13, 826 cases had been reported to the health department, only 312 fewer than the total of 1,138 cases reported for the entire year of 1959. Nationally, 8,160 cases were reported through March 19, with a total of 23,187 for 1959. The record high in Michigan was in 1954 when 1,419 cases were reported. The cases are scattered throughout the state and have been increasing since the fall of 1958 in keeping with the cyclic pattern of the disease, Dr. Leeder said. The increase during the first part of this year reportedly could be associated partially with the excessive moisture causing overflow of septic tanks and contaminating well water in suburban areas. There has been no contamination of regularly tested municipal water supplies, Dr. Leeder reported.

Annual Conference on Aging.—The University of Michigan will present its 13th annual Conference on Aging June 27-29 at the Michigan Union, Ann Arbor, under the theme "Aging in the 60's—Decade for Action." The work of the conference will center around development of plans for building national, state, and local programs drawn up by the White House Conference on Aging. Fields to be considered will be health, housing, income, employment, education, free time, social services, and institutional administration. Group discussion will be held on the following topics:

Organizing for Action.
Implementing Action.
Building Aging into the Social Structure.
Achieving Interaction.

Plenary sessions will include analysis of the processes of action and reports of the outcomes of group discussions. For information, write the University of Michigan, Division of Geriatrics, Extension Service, Ann Arbor, Mich.

MINNESOTA

Student Wins Rural Medicine Scholarship.—George Bruce Gerstenkorn, University of Minnesota Medical School freshman from Belgrade was named winner of the $4,000 Rural Medical Scholarship presented annually by the Minnesota State Medical Association. Mr. Gerstenkorn will receive $1,000 for school expenses each year for four years. In return, he promises to practice medicine for a period of at least five years after graduation in a Minnesota community in need of a doctor. Holder of a Minnesota Medical Foundation Scholarship, he becomes the eighth winner of the M. S. M. A. scholarship which is aimed at encouraging young physicians to practice in rural areas of Minnesota. In addition, the scholarship is designed to assist a "worthy and outstanding student" to meet the cost of medical education.

Hospital Addition Dedicated.—A $6,500,000 addition to St. Joseph's Hospital, St. Paul, was dedicated June 4. The new John Gregory Murray Unit, named in honor of the late archbishop of St. Paul, and staffed by the Sisters of St. Joseph of Carondelet, will bring the number of beds in the hospital to 430. The total will reach 500 beds on completion of remodeling of the present main section. More than $2,500,000 of the total cost has been contributed by the people of St. Paul, the remainder financed by the Sisters, who have served in the hospital since its founding 107 years ago. St. Joseph's is reportedly the oldest hospital in the state. The five-story, completely air-conditioned John Gregory Murray Unit includes an 82-bed surgical division, eight major operating rooms, four special operating rooms, one oversized room for cardiac surgery, and an emergency room surgery suite. New laboratory, pathology, and radiology departments are located in the new addition. Indoor and outdoor play areas are provided in the pediatrics department. Each patient area has two lounges for use of patients and visitors. Dr. Francis J. Braceland, Hartford, Conn., psychiatrist-in-chief of the Institute of Living and clinical professor of psychiatry at Yale University, gave the main address at a dedication dinner for the medical staff of St. Joseph's on June 3. The psychiatrist is president-designate of the International Catholic Association for Psychotherapists and Psychologists.

MISSISSIPPI

State Medical Election.—The Mississippi State Medical Association announced that the officers for 1960-1961 are: president, Dr. G. Swink Hicks, Natchez; president-elect, Dr. Lawrence W. Long, Jackson; secretary-treasurer, Dr. William E. Lotterhos, Jackson (1961); vice-presidents, (1961), Drs. Frank M. Davis, Corinth, Jack V. King, Jackson, and Charles R. Jenkins, Laurel; delegates to the American Medical Association, Drs. John P. Culpepper Jr., Hattiesburg (1961), and John F. Lucas, Greenwood (1962); alternate delegates, Drs. Braxton B. O'Mara, Biloxi (1961), and George E. Twente, Jackson (1962); and executive secretary, Mr. Rowland B. Kennedy, 735 Riverside Drive, Jackson, Miss.

MONTANA

Institute for Maternal and Newborn Care.—The Montana State Committee for Maternal and Newborn Care will hold its fourth annual institute at the Western Life Building, Helena, Thursday and Friday, July 14-15. Subject matter will be presented under the theme "Emotional Implications in Maternal and Newborn Care—New Emphasis on the Significance of Everyday Observations." Guest speakers will be Dr. Gordon D. Jensen, assistant professor of pediatrics, University of Washington; Dr. Thomas H. Kirschbaum, instructor in obstetrics, University of Utah; and Louise Murray, R.N., assistant professor of maternal and child care, University of Washington. For information, write Dr. David P. Findley, Medical Consultant, State Committee for Maternal and Newborn Care, Box 206, Capitol Station, Helena, Mont.

NEW JERSEY

Project on Taste Research.—A three-year-long research project underway at Rutgers University's laboratory of psychopharmacology is designed to determine whether the sense of taste changes as a person gets older. The Rutgers research project is being supported by a grant from the pharmaceutical firm of E. R. Squibb and Sons. During the experiments with the "taste threshold," the chemical concentration at which a person can detect the presence of a certain flavor, persons from 6 to over 60 will be studied.

NEW YORK

Amendment on Reporting Staphylococcal and Suppurative Diseases.—Cases of staphylococcal disease and suppurative disease occurring in hospitals in Upstate New York will become reportable July 1 under a new amendment to the New York State Sanitary Code. Joint letters from the Medical Society of the State of New York and the State Health Department have been sent to all physicians informing them of the action of the New York State Public Health Council. The council makes regulations of the Sanitary Code. The purpose of the amendment is to make immediately available to hospitals through prompt reporting the full scientific, epidemiological, and laboratory facilities of the State Health Department and local health departments in combatting staphylococcal disease.

Ophthalmologist Named Alumni Award Recipient.—Dr. Thomas M. d'Angelo, director of ophthalmology at Queens Hospital Center and at the Flushing Hospital and Dispensary, Flushing, was named a 1960 recipient of the New York University Alumni Meritorious Service Medallion. The annual awards are the "highest bestowed upon graduates by the Alumni Federation of the University." A bronze medal with the inscription "To Honor One Who Through Deeds Has Served Alma Mater" was presented to Dr. d'Angelo at NYU's 128th commencement June 8. Dr. d'Angelo has been chairman of the board of trustees of the Medical Society of Queens and is a former president of the society. He was president of the NYU Medical Alumni Association in 1953-1954.

Personal.—Dr. Granville W. Larimore, deputy commissioner, New York State Department of Health, has been appointed chairman of the 1961 National Health Forum, Dr. James E. Perkins, president of the National Health Council, which sponsors the annual forum on behalf of its more than 70 member agencies, announced. The 1961 National Health Forum to be held at the Waldorf Astoria Hotel in New York City, March 13-16, 1961, will consider "Health and Communication."——Dr. Vincent I. Bonafede, assistant director (administrative) at Craig Colony and Hospital in Sonyea, was appointed director effective May 1, according to an announcement by Dr. Paul H. Hoch, New York State commissioner of mental hygiene. Dr. Bonafede assumed the post on the retirement of the former director, Dr. George L. Warner.

Regulation for Footprinting Babies.—The New York State Public Health Council passed a regulation making footprinting of newborn infants mandatory, Dr. Herman E. Hilleboe, State Health Commissioner, announced. More than half of the hospitals in Upstate New York are presently footprinting newborn infants. "The Federal Bureau of Investigation, the New York State Department of Correction, and the American Academy of Pediatrics all agree that footprinting of newborn infants is of value in permanent identification, but only if proper techniques are used to obtain the prints," Dr. Hilleboe said. Institutes have been set up by the State Health Department regional health directors in cooperation with regional hospital councils to provide instruction for hospital staff members concerned with the techniques of taking footprints properly.

Study on Hospital-Community Relations.—A team of researchers from Cornell University will begin a study of hospital-community relations next month which will seek to relate opinions to definite hospital characteristics. The Cornell social scientists will cooperate with a research group from Syracuse University studying community leadership. Interviews will be conducted in the Syracuse metropolitan area to determine the attitudes and experiences of residents with various Syracuse hospitals. In addition, a sample of members of the county medical society will be polled to determine the kinds of hospitals that physicians like working in and the types which offer the best facilities in regard in nursing staffs and other services. Information compiled through this study will be compared with previous results obtained from 136 hospitals in Upstate New York.

New York City

University Promotions.—Faculty promotions at the State University of New York Downstate Medical Center in Brooklyn were announced May 7 by President Robert A. Moore, and the following persons were advanced to full professor: Dr. Stanley M. Aronson, associate professor of pathology; Dr. Irving F. Enquist, associate professor of surgery; Dr. Lawrence F. Frank, associate professor of dermatology, who will head the division of dermatology; and Dr. Brian F. Hoffman, associate professor of physiology.

Course for Prosthetic Technicians.—The Institute for the Crippled and Disabled in New York City is accepting applications for its 1960-1961 training courses for orthotic and prosthetic technicians. The nine-month courses will begin on Sept. 12, 1960, and end June 30, 1961. A fifth of each course will be devoted to academic instruction by professional members of the institute's staff and of New York University with which the institute is professionally affiliated. Clinical experience will be provided through field assignments at hospitals and other institutions working with the disabled. Applications and information may be obtained from the Director, Prosthetic and Orthotic Laboratories, Institute for the Crippled and Disabled, 400 First Ave., New York 10.

Appoint Chairman for Pediatric Department.—Dr. Saul Krugman, associate professor of pediatrics at New York University Medical Center, was appointed professor and chairman of the department of pediatrics at the center, effective July 1. He succeeds Dr. L. Emmett Holt Jr., who is retiring on June 30 to devote full time to his research activities as visiting physician-in-charge of the Children's Medical Service at Bellevue Hospital and as attending physician and director of the pediatric service at University Hospital. Dr. Krugman received his doctor of medicine degree from the Medical College of Virginia. He became an instructor at New York University School of Medicine in 1948, receiving successive appointments as assistant professor and associate professor prior to his present appointment.

Dr. Freedman Named Department Head.—Dr. Alfred M. Freedman was appointed professor and chairman of the department of psychiatry at New York Medical College. Dr. Freedman, associate professor of psychiatry, State University of New York, Downstate Medical Center, will assume his new post at the end of this academic year. In the past, Dr. Freedman served as clinical instructor in psychiatry at the New York University College of Medicine, psychiatric director of the League for Seriously Emotionally Disturbed Children, assistant in psychiatry at University Hospital, and senior psychiatrist of the Child Psychiatry Service of Bellevue Hospital. He was a delegate of the American Psychiatric Association to the 1960 White House Conference on Children and Youth in Washington, D. C.

Personal.—Dr. Daniel J. Feldman, associate professor of physical medicine and rehabilitation of New York University School of Medicine, visited Chile May 1-15 as a guest of the Chilean Society of Rehabilitation in Valparaiso and the Post Graduate Medical School of the University of Chile in Santiago. During his visit Dr. Feldman gave 10 lectures in Valparaiso and four lectures in Santiago covering major aspects of physical medicine and rehabilitation for medical and co-professional personnel.——Dr. Arthur A. Briskier was invited by the deans of the universities of Paris, Bordeaux, Marseilles, and Strasbourg to deliver during the months of April and May, a series of lectures on the universal method of charting the heart auscultation, and the radio and radiophoto transmission for instant consultation at any distance.

Rehabilitation Counseling Internship.—A vocational rehabilitation counseling internship program was announced May 23 by the Institute for the Crippled and Disabled. The internships are supported jointly by the Office of Vocational Rehabilitation, U. S. Department of Health, Education, and Welfare, and by the institute. Positions in the internship program are open to those who have completed the masters degree in vocational rehabilitation counseling, psychology, and related programs, and to those who are enrolled in third and fourth year doctoral programs in the same fields. Enrollment is limited to U. S. citizens. Stipends ranging from $3,000 to $4,200 per year are provided to those accepted for enrollment. The specific amount of individual stipends will vary with the availability of funds and with the educational attainments of the intern. For information, write Wilfred Haber, Chief of Vocational Rehabilitation Counseling Service, Institute for the Crippled and Disabled, 23rd Street and First Ave., New York 10.

Conference on Rehabilitation of the Mentally Retarded.—The department of psychological foundations and services, Teachers College, Columbia University, and the Association for the Help of Retarded Children, Inc., will present a work conference on "Rehabilitation of the Adolescent and Adult Mentally Retarded—Psychological and Vocational Approaches" July 11-22 at the AHRC Training Center & Workshop, and the Teachers College. The conference will focus on the "philosophy, principles, and techniques in the rehabilitation of the mentally retarded." Emphasis will be placed on the role of the sheltered workshop as a major resource in a total community rehabilitation program. Students will be assigned to special trainees under staff supervision, with opportunities for active participation in vocational evaluation, individual and group counseling, job training, and other aspects of the center program. Lectures and group discussions will supplement the assignments. Stipends are available. For information, write the Coordinator of the Conference Program, Abraham Jacobs, Ph.D., Box 35, Teachers College, Columbia University, New York 27.

NORTH CAROLINA

Report on Accidental Deaths.—Home and farm accidents claimed the lives of more North Carolina residents during March than in any month since February, 1958. The toll for March was 101 deaths. As of May, home and farm accidents caused 258 resident deaths. Home and farm accidental deaths for the first three months of 1960 exceeded motor vehicle deaths by seven. All accidents caused 612 deaths during the first three months of 1960.

PENNSYLVANIA

Philadelphia

Research Building Named for Dr. Richards.—The $3,100,000 Alfred Newton Richards Medical Research Building of the University of Pennsylvania School of Medicine was dedicated May 19 at special ceremonies on the university campus. The seven-story, four-tower structure is named for Alfred Newton Richards, Ph.D., emeritus professor of pharmacology and former vice-president of the university for medical affairs. Three 45-ft. square laboratory "studios" are situated on each level of the building, one in each of three towers, with all utilities and general services centered in the fourth, or central tower. Guest speakers for the dedication ceremonies were Dr. Richard E. Shope, of the Rockefeller Institute, and Dr. John D. Porterfield, III, deputy surgeon general, U. S. Public Health Service. The building was financed by the university and the U. S. Public Health Service, which contributed $1,500,000 in matching funds under the Federal Health Research Facilities Act. It will be occupied by the departments of microbiology; the Harrison Department of Surgical Research; part of the department of physiology and the Henry Phipps Institute section of the department of public health and preventive medicine; and the Johnson Foundation for Medical Physics.

Alfred Newton Richards Medical Research Building, dedicated in May, as seen from the south end of the University of Pennsylvania campus, Philadelphia.

WEST VIRGINIA

Appoint Dr. Flink Department Chairman.—Appointment of Dr. Edmund B. Flink, of Minneapolis, as professor and chairman of the department of medicine at West Virginia University was announced. Dr. Flink, professor of medicine at the University of Minnesota and chief of medical services at the Minneapolis Veterans Hospital, will join the West Virginia staff this summer. Dr. Flink, an internist, earned M.D. and Ph.D. degrees at the University of Minnesota. In 1948-1949, he studied in the Harvard Medical School's department of biological chemistry under a Commonwealth Fund Fellowship and in 1957-1958 served as a visiting professor at Seoul (Korea) National University.

Personal.—Dr. Robert Paul Hagerman, superintendent of Weston State Hospital, was named by Governor Cecil H. Underwood as director of the State Department of Mental Health to succeed Dr. Richard J. Lilly, who is engaged in the private practice of psychiatry at Parkersburg.——Dr. Frank V. Langfitt, Clarksburg surgeon, was given the honorary degree of doctor of humanities by Salem College. The award was made during commencement exercises late in May. Dr. Langfitt is past-president of the Harrison County Medical Society and the West Virginia State Medical Association.

WISCONSIN

State Medical Election.—The Wisconsin State Medical Society has elected the following officers: president-elect, Dr. Leif H. Lokvam, Kenosha; speaker of the house of delegates, Dr. Eugene J. Nordby, Madison; vice-speaker, Dr. Norbert A. McGreane, Darlington (reelected); delegates to the A. M. A., Dr. Lien O. Simenstad, Osceola (reelected), Dr. Ervin L. Bernhart, Milwaukee (reelected); alternates, Dr. John M. Bell, Marinette (reelected), and Dr. James M. Sullivan, Milwaukee (reelected). Dr. Edmund D. Sorenson, Elkhorn, was installed as president, succeeding Dr. William B. Hildebrand, Menasha.

Personal.—Dr. Francis M. Forster, chairman, department of neurology, University of Wisconsin School of Medicine, Madison, was elected president of the American Board of Psychiatry and Neurology. Dr. Forster has served as a director of the board since 1952 and has been representing the American Neurological Association on the board. ——Dr. Mynie G. Peterman, Milwaukee, was invited to lecture at the University of Madrid, Spain, where he will receive an honorary degree. He will also address the annual meeting of the Madrid Pediatric Society on "Epilepsy in Children."

GENERAL

Committee to Study Health Agencies.—The Rockefeller Foundation announced the formation of an ad hoc committee to make an exploratory study of the role and responsibilities of voluntary health and welfare agencies in the United States. The committee is undertaking the study at the invitation of the foundation. The chief question the committee will decide is whether a later, more comprehensive study of voluntary health and welfare agencies would be feasible and in the public interest. The committee expects to complete its recommendations and report by the end of the year. Dr. Robert H. Hamlin, Boston, is study director.

Cancer Seminar for Southeastern States.—The 10th biennial Southeastern States Cancer Seminar for Physicians will be held at the Cherry Plaza Hotel, Orlando, Fla., Nov. 16-18. The theme, "New Horizons of Cancer Research and Therapy," will feature a faculty of 14 guest speakers. The seminar is being presented by the Orange County Medical Society in cooperation with the Florida Medical Association and supported jointly by the Florida State Board of Health and the American Cancer Society, Florida Division, Inc. There is no registration fee. For advance reservations or information, write the 1960 Cancer Seminar Committee, 17 Lake St., Orlando, Fla.

Trudeau Society Changes Name.—The American Trudeau Society has changed its name to the American Thoracic Society by action of its membership at the annual business meeting May 17 in Los Angeles. The society was organized in 1905 as the American Sanatorium Association. It was reorganized in 1939 as the American Trudeau Society, named in honor of the first president of the National Tuberculosis Association, Dr. Edward Livingston Trudeau. The ATS, which has a membership of more than 5,000 physicians and other scientists with a major interest in tuberculosis and other respiratory diseases, is the medical section of the National Tuberculosis Association.

Invite Applications for Research Awards.—The Life Insurance Medical Research Fund is receiving applications for two types of awards to be available July 1, 1961, as follows: (1) Until Oct. 15, 1960, for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend is $4,500 with allowances for dependents and necessary travel. (2) Until Nov. 1, 1960, for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 E. 46th St., New York 17.

Nutrition Team Aiding in Chile Emergency.—A U. S. Nutrition Team is remaining in Chile during that country's present emergency, the Department of Defense announced May 25. Dr. Francis B. Berry, Washington, D. C., assistant secretary of defense (health and medical), and chairman of the U. S. Interdepartmental Committee on Nutrition for Defense, said that the Nutrition Team's stay in Chile has been extended and its services will be made available to the government of Chile through the United States Embassy there. The U. S. team was concluding its work and was scheduled to return home when earthquakes and floods struck the Latin American country. The team had been in Chile for two months, working with the government of Chile in cooperation with the World Health Organization; Food and Agriculture Organization of the United Nations; U. S. International Cooperation Administration; and the U. S. Military Assistance Advisory Group in Chile.

Traffic Fatalities Rise in April.—The highway death toll in the U. S. went up 10% over the toll for the same month last year, the National Safety Council reported. This was the greatest such monthly increase since June, 1956. The April total of 2,910 traffic fatalities not only was 260 more than the toll of 2,650 for the same month last year, but was the largest for any April since 1957, when the death toll was 2,933. Disabling injuries from traffic accidents in April were estimated by the council at 400,000. The sharp rise in April was a drastic change from the 16% decrease in traffic deaths recorded in March from the same month a year ago. Traffic deaths at the end of the first four months of this year were only 1% below those for the same period last year—10,590 against 10,730. Deaths had been 5% below last year at the end of the first three months of this year. Motor vehicle travel was up 4% in the first four months of this year over the same period last year, the council said.

Deaths in Tornadoes, Hurricanes, and Floods.—According to Metropolitan Life Insurance Company statisticians, tornadoes, hurricanes, and floods took about 3,100 lives in continental United States during the 10-year period 1950-1959. Tornadoes were the worst killers during this period, accounting for about 1,400 deaths, or 45% of the total. Hurricanes and floods shared about equally in the other lives lost. The annual mortality from hurricanes fluctuates to a greater extent than that from tornadoes and floods, the statisticians point out on the basis of Weather Bureau reports. There were only 10 deaths from hurricanes during 1959, and not a single fatality the year before. The only hurricane to strike the United States during 1957 resulted in the heaviest loss of life from any natural disaster in the last 20 years. Floods accounted for 834 deaths in the 1950-1959 decade. For each year except 1955, the loss of life was less than 100. In 1955, nearly 200 persons perished in the floods resulting from the rains accompanying a hurricane that struck the Northeastern part of the country on Aug. 17-19.

Students Win Scholarships for Allergy Research.—The Allergy Foundation of America announced the awarding of its $600 summer scholarships for 1960 to 30 medical students from medical schools throughout the United States and Canada so that these students might spend 8-12 weeks obtaining supervised training and experience in both clinical and research allergy. This is the largest number of these awards made by the foundation during any year since the scholarship program was begun in 1956. These awards are intended "to encourage and assist medical students to obtain a broader knowledge and better understanding of the allergic diseases." The recipients participate actively in research in allergy or in the basic sciences related to allergy. The students selected were nominated by the deans of their respective medical schools in collaboration with the heads of basic science departments at these institutions. The Allergy Foundation of America, with headquarters at 801 Second Ave., New York City, was established in 1953 to promote medical education and research in allergy and to provide the public with authoritative information and advice in this field.

Approve Grants for Heart Research.—With 216 newly approved research grants-in-aid, the American Heart Association will spend a new high of more than 9 million dollars for scientific studies to combat diseases of the heart and blood vessels during a 12-month period beginning July 1, Dr. A. Carlton Ernstene, Cleveland, association president, announced. Although this is the largest research allocation ever made by the association, Dr. Ernstene said 45 "worthy projects" cannot be financed for lack of funds. Support of research is made possible by public contributions to the annual Heart Fund appeal. Of the 9 million dollars, local heart association awards to underwrite scientific studies in their areas account for an estimated $5,500,000. Awards by the American Heart Association's national research committee exceed $3,600,000, with newly approved national grants-in-aid for 216 research projects totaling almost $1,700,000 included. More than half of these awards cover 114 new applications while 102 will continue support for research projects in progress. Fellowships and grants totaling almost $1,900,000 awarded to 171 research scientists were announced earlier this year. Of the grants announced, Dr. Ernstene said that hardening of the arteries is a major target.

Meeting on Deafness.—A four-and-a-half day program of talks, panel discussions, demonstrations, and business meetings has been arranged for the 1960 summer meeting of the Alexander Bell Association for the Deaf in Rochester, N. Y., June 26-July 1. The keynote address by association president George T. Pratt at the opening session June 27 will set the theme for the following days. Teaching speech to the deaf will be the topic that day. Language is the topic to be considered in talks, demonstrations, and panel discussions on Tuesday, June 28. The morning of June 29, 16 invited papers will be presented at three concurrent sessions. A trip to Niagara Falls and one to the Speech and Hearing Center of Syracuse University are planned for the afternoon. Parents' Day will be June 30, with speakers, panel discussions, elections, and a luncheon. Dr. John J. Lee, chairman, department of special education and vocational rehabilitation, Wayne State University, will be the speaker at the annual banquet that evening. At the closing session guidance and adjustment will be the topics under discussion. Preregistration blanks are available and may be obtained by writing to the Alexander Graham Bell Association for the Deaf at 1537 35th St., N. W., Washington 7, D. C.

Establish Pharmacology Award.—The establishment of the Torald Sollmann Award for achievements in pharmacology was announced April 12 by Dr. Louis S. Goodman, Salt Lake City, Utah, president of the American Society of Pharmacology and Experimental Therapeutics, during the annual business meeting of the organization. Dr. Goodman revealed that the award, to be sponsored by Wyeth Laboratories, Philadelphia pharmaceutical manufacturing concern, will be given for "significant contemporary contributions to the advancement and extension of knowledge in the field of pharmacology." The Sollmann Award will consist of a $2,500 honorarium, a scroll, and a medal. The recipient will deliver the Sollmann Oration, covering his major contributions to pharmacology, at the organization's fall meeting. The award is named for Dr. Sollmann, of Cleveland, in commemoration of his "vital, pioneer efforts in furthering pharmacological investigation and education in the United States." Dr. Sollmann was professor of pharmacology at Western Reserve University School of Medicine, Cleveland from 1906 to 1946. He served also as dean of the school from 1928 until 1944. Dr. Sollmann retired as chairman of the American Medical Association's Council on Drugs last December, after more than 50 years of service. Nominations for the Sollmann Award may be made by members of the society or any other national or international scientific organization with a limitation of one nominee to be proposed by any one group or individual.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	May 21, 1960		May 23, 1959
	Paralytic Type	Total Cases	Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	1	1	..
Rhode Island	..	..	..
Connecticut	..	..	..
Middle Atlantic States			
New York	1	1	..
New Jersey	..	..	..
Pennsylvania	..	..	..
East North Central States			
Ohio	..	..	5
Indiana	..	..	..
Illinois	..	..	..
Michigan	..	..	..
Wisconsin	..	..	..
West North Central States			
Minnesota	..	..	2
Iowa	..	..	..
Missouri	1	1	1
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	..	..	1
Kansas	..	..	1
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	2
West Virginia	..	..	..
North Carolina	..	..	..
South Carolina	..	..	1
Georgia	..	..	1
Florida	1	1	5
East South Central States			
Kentucky	..	..	..
Tennessee	1	1	1
Alabama	..	..	..
Mississippi	2	2	..
West South Central States			
Arkansas	..	..	..
Louisiana	2	2	..
Oklahoma	..	..	1
Texas	1	2	9
Mountain States			
Montana	..	2	..
Idaho	..	..	..
Wyoming	..	..	..
Colorado	..	..	..
New Mexico	..	..	..
Arizona	..	..	5
Utah	..	..	..
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	..	..	1
California	3	4	2
Alaska	..	..	..
Hawaii	..	..	..
Territories and Possessions			
Puerto Rico	9	9	..
Total	22	26	38

Announce Medical Faculty Awards.—Fourtee promising medical school faculty members wer named to share $250,000 under the Medical Facult Awards program of Lederle Laboratories Divisio American Cyanamid Company. Dr. Benjamin W Carey, Lederle medical director, stated in announ ing the annual wards that their purpose is "t assist able young men and women who are wor ing and contemplating further full-time academ careers in the preclinical and certain clinical departments of medical schools; to enable these departments to offer opportunities for favorable development of promising individuals as members of the full-time faculty and to provide recognition, encouragement, and incentive for outstanding clinical teachers and scholars." Over the seven-year span of the grants, more than $1,750,000 has gone to 105 faculty members in 55 United States and Canadian medical schools. Winners of the awards this year were:

Dr. George L. Jordan Jr., Baylor University; Dr. E. Lovell Becker, Cornell University; Dr. Robert P. Heaney, Creighton University; Dr. Mortimer Lorber, Georgetown; Dr. Elizabeth D. Hay, Harvard University; Julius J. Friedman, Ph.D., Indiana University; Dr. Harold P. Schedl, State University of Iowa; Bernard Roizman, Sc.D., Johns Hopkins; Dr. Kingsley M. Stevens, University of Kentucky; Dr. Paul F. Smith, University of Pennsylvania; John T. Matschiner, Ph.D., St. Louis University; Stefan Kruger, Ph.D., Tulane University; Dr. Elmer B. Brown Jr., Washington University; and George W. Brown Jr., Ph.D., University of Wisconsin.

The awards, generally made for terms not exceeding three years, fall into three categories: (1) to supplement the salary of an individual, so that the school can retain him for vital teaching and research functions; (2) to bring into the school a new faculty member not previously supported either by budget or research funds; and (3) to continue the salary of an individual previously supported from sources outside the medical school, such as research fellowships or grants.

LATIN AMERICA

Course in Nasal Surgery in Mexico City.—Thirty-six surgeons from the United States will be included in the faculty that will present a two-weeks' postgraduate course, "Reconstructive Surgery of the Naval Septum and External Pyramid," beginning July 4 at the Universidad Nacional Autonoma de Mexico, Facultad de Medicina, Mexico, D. F. Dr. Maurice H. Cottle, professor of rhinootolaryngology at the Chicago Medical School, will be the guest professor, it was announced by Prof. Andres Bustamente Gurria, professor of rhinootolaryngology at the Mexican university. The American Rhinologic Society, founded by Dr. Cottle, will cooperate. Classes will be held from 8 a. m. until after 10 p. m. Scientific exhibits will be displayed. For information, write to Dr. Robert M. Hansen, Secretary, American Rhinologic Society, 1735 N. Wheeler Ave., Portland 17, Ore.

Symposium on Staphylococci in Buenos Aires.—Under the patronage of the Faculty of Medical Sciences of Buenos Aires and with the financial support of the Roemmers Foundation, a Symposium on Staphylococci is being organized by Prof. Dr. J. M. Leston (epidemiology and clinical aspects) and Prof. Dr. C. Rechnievski (bacteriology and immunology) for July 14-16. The purpose of the symposium is to assemble international and local experience on staphylococci concerning visceral localization, characteristics of resistant strains, growing lack of sensitivity to different antibiotics, immunological problems, increase of frequency of staphylococcal infections, and orientations for prevention and treatment. The program will be organized in a sequence of plenary subsymposiums and communication sessions. Clinicians, epidemiologists, and laboratory workers, are invited to contribute to the symposium. Following presentation at the program, the papers will be published in a special volume. For information, write the Secretary, M. E. Jörg, Corrientes 316, Esc. 153, Buenos Aires, Argentina.

FOREIGN

Hematology Meeting in Tokyo.—The Eighth International Congress of Hematology organized by the International Society of Hematology and the Science Council of Japan will be held in Tokyo Sept. 4-10 at Sankei-Kaikan. The main subjects of the scientific sessions will be as follows:

Nucleonics.
Leukemia.
Hemocytology.
Anemia.
Coagulation and Hemorrhagic Disorders.
Immunohematology.

Several symposiums concerning the main subjects are planned. The working languages of the Congress will be English, French, and Japanese. Technical and commercial exhibits are planned and excursions are arranged. For information, write the Secretary General, Western Hemisphere, Dr. James L. Tullis, 1101 Beacon St., Brooklyn 46, Mass.

Pathology Meeting in London.—The third International Congress of the International Academy of Pathology will be held June 20-24 at the Royal College of Surgeons of England, London, W. C. 2. The scientific program will open with a symposium on leprosy research the morning of June 20. Four papers will be presented June 21 at a symposium, "Total Body Radiation." At the June 22 session, 15 papers are scheduled for presentation. A symposium and panel discussion, "Thyroiditis: Classification and Modern Concepts," will include the following topics:

Classification.
Experimental Thyroiditis.
Lymphocytic Goiter.
Immunology.
Pathogenesis and Therapeutics.

A panel discussion on Thyroid Cancer June 24 will be followed by a question-and-answer period. Exhibitions and a program of tours are planned. For information, write Prof. George Cunningham, Royal College of Surgeons, Lincoln's Inn Fields, London W. C. 2, England.

Congress of Nephrology.—The first International Congress of Nephrology will be held in Geneva, Switzerland, Sept. 1, and Evian, France, Sept. 2-4. The official languages of the congress will be French and English and simultaneous translation will be available during plenary sessions and round-table discussions. Subjects for the plenary sessions include the following:

Regulation of Tubular Ionic Exchange.
Shock Kidney.
 (a) Mechanism of Renal Lesions Induced by Shock.
 (b) Treatment.
Recent Advances in Nephrology.

Round-table sessions will be held on glomerular ultrastructure, and stop flow techniques and diuretics. A conference titled "Kidney Transplantation in Man" is planned for the morning of Sept. 2. A program of social events is planned. The congress is organized by the Scandinavian Society for Kidney Research, American Society for Clinical Investigation, Societa Italiana Di Nefrologica, and the Renal Association. For information, write Prof. Agrégé Gabriel Richet, Hôspital Necker, 149 Rue de Sévres, Paris 15eme, France.

CORRECTION

Dr. McCrae Is President-Elect of Urological Section.—The Director of Public Relations, Temple University Medical Center, Philadelphia, has written that "due to a typographical error our report as published in the May 14th issue [Medical News, p. 187] was in error. Dr. Lowrain E. McCrae was named president-elect of the Middle Atlantic Section of the American Urological Association."

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Dermatology: *Final date for filing* applications of candidates completing training by October 15, 1960 is March 1, 1961. *Written.* Several cities, June 5, 1961. *Oral.* Philadelphia, Oct. 13-16, 1961. Sec., Dr. Maurice J. Costello, One Haven Avenue, New York 32, New York.

American Board of Internal Medicine: New York City, Nov. 14-17. Closing date for filing application is July 1. *Written.* Oct. 17. Closing date for filing application was May 1. Schedule for 1961. *Written Examination,* October 16. *Oral Examinations.* New Orleans, Jan. 30-Feb. 2; Chicago, April 4-7; Los Angeles, Sept. 26-29; New York City, Nov. 7-10. Closing date for acceptance of applications for the January and April examinations is October 1, 1960, and for the September and November examinations is June 1, 1961. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. *Oral.* New Haven, Nov. 6-9. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: Applications for certification in Part I, new and reopened, are now being accepted. Deadline for receipt of applications is August 1, 1960. *Oral Examination, Part II.* Chicago, April 7-14, 1961. Final date for filing application is August 1, 1960. After July 1, 1962, a minimum of three years of approved progressive residency training will be required. Training by preceptorship will no longer be acceptable. The initiation of preceptorships will not be approved after July 1, 1960. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

American Board of Orthopaedic Surgery: *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing application is July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral.* Chicago, Oct. 3-6. Final date for filing application was April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Proctology: *Oral and Written, Parts I and III.* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: New York, New York, Dec. 12-13, New Orleans, Mar. 20-21, 1961. Sec., David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnati, Dec. 10-13. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination is July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Written.* (Part 1), Various Centers, Dec. 7. *Candidates are urged to apply several months before completion of training requirements.* The closing date for filing applications is August 1. Those completing training requirements after September 30 cannot be considered for the December Part I examination of the same year. *Oral.* (Part II)—New Haven, Sept. 26-27; Indianapolis, Oct. 24-25; Buffalo, Nov. 14-16; Nashville, Dec. 12-13; Philadelphia, Jan. 16-17; Houston, Feb. 13-14; Columbus, Ohio, Mar. 13-14; New York City, April 19-20; Portland, Ore., May 15-16; San Francisco, May 18-19. No examinations will be held in June, July or August. Sec.-Treas., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

Board of Thoracic Surgery: *Written.* Various centers throughout the country, Sept. 9. Final date for filing application is July 1. *Oral.* Oct. 1960. Final date for filing application is July 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

GOVERNMENT SERVICES

FOOD AND DRUG ADMINISTRATION

Honey-Vinegar "Health Cocktail" Seized.—A honey and apple cider vinegar mixture neither promotes health nor prolongs life. More than 5,000 cases of the mixture were seized on charges that it was misbranded because the label failed to bear adequate directions for use in the many disease conditions for which it was intended. Directions for use cannot be adequate if the product will not be effective when the directions are followed. In his sales literature the promoter prominently referred to the best-selling book entitled "Folk Medicine," by Dr. D. C. Jarvis. The physician recommended honey and vinegar for specific conditions in his book, and described the benefits found in his experience, but he had no knowledge of, or connection with, sales of the product.

Although the container label offered the product merely as a "tune-up drink" and food seasoning, the reference to the book could only mean that it was offered as a cure for the diseases for which the book claims it to be effective, including digestive disorders, constipation, obesity, high blood pressure, heart disease, chronic fatigue, headaches including migraine headaches, all infectious diseases, all childhood diseases, diabetes, insomnia, sterility, difficult labor and morning sickness, and nervousness.

Food Seizures.—In March, rodent contamination in carload shipments of wheat and flour caused the seizure of 278 tons. A total of 575 tons of unfit foods was removed from the market during the month. The second largest category consisted of 130 tons of nuts seized on charges they were spoiled, shriveled, moldy, and contaminated with filth. Eleven tons of a single producer's cheddar cheese were seized as an economic cheat on the basis that the product failed to comply with the federal standard for cheddar cheese, specifically in that the milk used was not pasteurized and the cheese had not been cured at a temperature of 35 F for 60 days. Such requirements are enforced for consumer protection, and any standardized food not meeting them is substandard and illegal.

Industry Aids in Consumer Protection.—A California nut packer voluntarily replaced an old building and equipment difficult to keep clean and provided improvements, including corrugated metal instead of wooden bins, steel drums instead of wooden boxes for temporary storage of walnut meats, and new stainless steel grading and conveying equipment. In March, 16 individual plants made voluntary improvements totaling $72,736, to assure production of clean, wholesome food products. Six hundred twenty-two tons of unfit food products were prevented from reaching consumers because their owners, in 61 additional voluntary actions, destroyed or converted them to nonfood use.

NATIONAL SCIENCE FOUNDATION

Postdoctoral Fellowships.—Applications will be accepted through Oct. 10 by the National Science Foundation for about 75 fellowships under the Senior Postdoctoral Fellowship programs. The awards will include medical sciences. To be eligible for Senior Postdoctoral Fellowships, the applicant must be a citizen of the United States, possess special aptitude for advanced training, and must have held the doctoral degree for at least five years or have equivalent education and experience. Senior postdoctoral fellows will be selected on the basis of ability as evidenced by letters of recommendation and other attestations of scientific attainment.

Applicants' qualifications will be evaluated by carefully chosen panels of scientists appointed by the National Academy of Sciences-National Research Council. Annual stipends to a maximum of $12,000, adjusted to match as closely as feasible the salaried income of the recipients at the time of application, will be awarded under this program. Fellows may engage in study and/or research at any appropriate United States or foreign nonprofit institution. A limited allowance to aid in defraying the cost of travel for a fellow and his dependents will also be available. Application materials may be obtained from the Fellowships Section, division of scientific personnel and education, National Science Foundation, Washington 25, D. C. Completed materials must be received not later than Oct. 10, 1960. All applicants will be notified by letter on Dec. 12, 1960, as to the disposition of their applications.

PUBLIC HEALTH SERVICE

Staff Changes.—Four key changes in the staff of the National Institutes of Health will become effective July 1. Dr. Joseph E. Smadel, presently associate director for intramural research, will become chief of the laboratory of virology and rickettsiology in the division of biologics standards. Dr. G. Burroughs Mider, now associate director in charge of research, National Cancer Institute, will replace Dr. Smadel as director of laboratories and clinics. Dr. Jack Masur, director of the clinical center, will be given additional staff responsibility for policy guidance and program planning within the office of the director as associate director for clinical care administration. Dr. Ernest M. Allen, chief of the division of research grants, will be given similar additional responsibility as associate director for research grants.

DEATHS

Anderson, Susan, Fraser, Colo.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1897; died in Denver April 16, aged 90, of cerebral infarction.

Bacon, Edison Pierce Ⓜ Santa Monica, Calif.; University of Southern California School of Medicine, Los Angeles, 1940; interned at the Los Angeles County Hospital, where he served a residency; member of the American Academy of General Practice; died Feb. 18, aged 52, of cerebral hemorrhage.

Bell, Joseph Clark Ⓜ Louisville, Ky.; born in Frostburg, Pa., Aug. 10, 1892; Harvard Medical School, Boston, 1923; interned at the Presbyterian Hospital in New York City, where he served a residency; professor of radiology at the University of Louisville School of Medicine; specialist certified by the American Board of Radiology; member of the American Roentgen Ray Society, Radiological Society of North America, of which he was past-president, and the American College of Radiology, of which he was a board member; a founder and past-president of the Kentucky Radiological Society; past-president of the Jefferson County Medical Society; veteran of World Wars I and II; a board member of the Blue Cross–Blue Shield; consulting radiologist at the Kosair Crippled Children Hospital; senior consulting radiologist at the Veterans Administration Hospital; associated with the Norton Memorial Infirmary, where he died April 25, aged 67, of rheumatic heart disease with mitral insufficiency.

Blanton, William Preston Ⓜ Juneau, Alaska; born in Buda, Texas, June 20, 1902; University of Colorado School of Medicine, Denver, 1933; interned at the Swedish Hospital in Seattle; served the Alaska Territorial Medical Association as secretary from 1934 to 1953 and was elected president the following year; a district councilor of the Alaska State Medical Association and vice-president of the Juneau District Medical Association; served as United States jail physician for many years, and was the designated physician for the Alaska Juneau Mining and Standard Oil Companies of Juneau since 1934; served as state medical director of the American Cancer Society; past-president of the Juneau Rotary Club; died in St. Ann's Hospital April 4, aged 57.

Blue, Waylon, Sanford, N. C.; born in Carthage, Dec. 3, 1898; Medical College of Virginia, Richmond, 1925; past-president of the Fifth District of the Medical Society of the State of North Carolina; for 18 years a member of the county board of education; an alderman for the town of Jonesboro, and past-president of the Sanford Rotary Club; a trustee of the Davidson (N. C.) College; on the staff of the Lee County Hospital; died in the North Carolina Memorial Hospital, Chapel Hill, April 13, aged 61, of infectious hepatitis.

Brager, Simon Ⓜ Baltimore; born in Baltimore, July 1, 1903; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1928; veteran of World War II; member of the Southeastern Surgical Congress; fellow of the International College of Surgeons and the American College of Surgeons; for many years secretary of the University of Maryland School of Medicine Alumni Association; assistant professor of surgery at his alma mater; served an internship and residency at the Mercy Hospital, where he remained associated throughout his career; on the staffs of the Sinai Hospital and Church Home and Hospital; died April 23, aged 56, of arteriosclerotic heart disease.

Cain, William Joseph, Madison, Wis.; Marquette University School of Medicine, Milwaukee, 1954; interned at the Jackson Memorial Hospital in Miami, Fla.; served a residency at the Milwaukee Children's Hospital in Milwaukee; died April 14, aged 32, of coronary disease.

Cohen, Frank Ⓜ Tucson, Ariz.; Columbia University College of Physicians and Surgeons, New York City, 1903; specialist certified by the American Board of Pathology; founding fellow of the College of American Pathologists; veteran of World War I; for many years practiced in Quincy, Ill., where he was on the staffs of the Blessing and St. Mary's hospitals; formerly pathologist at the Pima County General Hospital; died in Tucson Medical Center April 18, aged 80, of arteriosclerotic heart disease.

Cole, Frederick Herman, Detroit; born in Morenci, Mich., May 7, 1885; Detroit College of Medicine, 1908; specialist certified by the American Board of Urology; member of the American Urological Association; served as a member of the state board of registration in medicine; a member of the Detroit Public Welfare Commission from 1938 to 1941; formerly on the faculty of Wayne State University College of Medicine; served on the staffs of the Receiving, Highland Park, Harper, and Herman Kiefer hospitals; died in Natchez, Miss., April 14, aged 74, of cerebral thrombosis, and diabetes mellitus.

Coleman, Austin Hoffman, Miami, Fla.; Jefferson Medical College of Philadelphia, 1911; formerly practiced in Clinton, N. J., and was on the staffs of the Somerset Hospital in Somerville, N. J., and the Hunterdon Medical Center in Flemington, N. J.; died in Deerfield Beach March 21, aged 72, of cerebral thrombosis.

Corry, John James, Denver; Denver and Gross College of Medicine, 1906; died in the Colorado State Hospital, Pueblo, April 11, aged 85, of bronchopneumonia.

McKaig, Carle Beswick, Pine Island, Minn.; born in Warsaw, Ind., June 24, 1882; Sioux City (Iowa) College of Medicine, 1906; past-president of the Olmsted County Medical Society and of the Southern Minnesota Medical Society; served as a member of the school board for 27 years and as president for 25 years; for many years village health officer; served as chief of staff of the Zumbrota (Minn.) Community Hospital; on June 26, 1955, was honored by area residents and visitors at a "Doc McKaig Day" for professional and civic services to the community; died in St. Mary's Hospital, Rochester, Minn., March 20, aged 77, of pulmonary embolism and cerebral hemorrhage.

McKee, Clarence Stiles, Lutz, Fla.; University of Pennsylvania School of Medicine, Philadelphia, 1915; certified by the National Board of Medical Examiners; died in Tampa, May 3, aged 68.

Mebane, Donald Cummins Ⓢ Toledo, Ohio; Columbia University College of Physicians and Surgeons, New York City, 1920; interned at the Evanston (Ill.) Hospital; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; staff member of the Flower Hospital, Maumee Valley Hospital, Mercy Hospital, and the Toledo Hospital, where he died April 12, aged 66, of coronary thrombosis.

Miner, James Barzeal Sr. Ⓢ Charles City, Iowa; State University of Iowa College of Medicine, Iowa City, 1930; interned at the San Diego County General Hospital in San Diego, Calif.; past-president of the Floyd County Medical Society; past-president of the Charles City Lions Club; served as director of the Chamber of Commerce; on the staff of the Cedar Valley Hospital, where he died April 7, aged 55, of coronary occlusion.

Moe, Ralph Holbert, Griswold, Iowa; Creighton University School of Medicine, Omaha, 1948; member of the American Academy of General Practice; on the staffs of the Jennie Edmundson Memorial Hospital and Mercy Hospital, Council Bluffs, where he died April 1, aged 45, of myocardial infarction.

Morrison, William Wallace Ⓢ New York City; born in Plattsville, Ont., Canada, July 20, 1894; Western University Faculty of Medicine, London, Ont., Canada, 1919; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological Association, and the American Laryngological, Rhinological and Otological Society; interned at the Bellevue Hospital and New York Eye and Ear Infirmary, where he was a staff member; served with the Canadian Army during World War I; veteran of World War II; professor in the department of otolaryngology, New York Polyclinic Medical School and Hospital and associate professor of clinical otology at the New York University Post-Graduate Medical School; author of "Diseases of the Nose, Throat and Ear"; died April 17, aged 65, of coronary thrombosis.

Mulkey, Quinney Arnold Ⓢ Millen, Ga.; University of Georgia Medical Department, Augusta, 1909; fellow of the International College of Surgeons; served as president of the state board of medical examiners and Jenkins County Medical Society; veteran of World War I; medical director and administrator of the Mulkey Hospital, where he died April 7, aged 74, of acute coronary occlusion.

Nilson, Siegfried Johannes Ⓢ New York City; born in 1883; Columbia University College of Physicians and Surgeons, New York City, 1912; also a D.D.S.; member of the Industrial Medical Association, American Public Health Association, Association for the Advancement of Industrial Medicine and Surgery, and the American Association for the Advancement of Science; since 1957 medical director emeritus of the America Fore Loyalty Group Insurance Companies which he joined in 1912 as a medical advisor; in 1918 appointed medical director and in 1952 was appointed a vice-president; died in St. Luke's Hospital April 25, aged 76, of cerebral arteriosclerosis.

Nowland, George Dunn, Ashland, Maine; Baltimore University School of Medicine, 1896; died in Reno, Nev., April 10, aged 90, of arteriosclerotic heart disease.

Owens, Frederick Thomas, Utica, N. Y.; Johns Hopkins University School of Medicine, Baltimore, 1907; a captain in the medical reserve corps during World War I; served on the board of education; associated with St. Luke's–Memorial Hospital Center; died in Utica State Hospital April 8, aged 77, of hemorrhagic pancreatitis and enteritis.

Pack, Charles Edgar Jr. Ⓢ Memphis, Tenn.; University of Tennessee College of Medicine, Memphis, 1940; interned at St. Joseph's Hospital; served a residency at the Methodist Hospital; veteran of World War II; associated with the LeBonheur Children's Hospital, St. Joseph Hospital, Baptist Hospital, and the Methodist Hospital, where he died April 13, aged 47, of coronary disease.

Paul, Daniel Frank Ⓜ Rock Island, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1917; member of the American Academy of General Practice; veteran of World War I; associated with St. Anthony's Hospital, where he died April 10, aged 69, of uremia.

Pennington, John, Ventnor, N. J.; Jefferson Medical College of Philadelphia, 1916; veteran of World War I; associated with the Atlantic City (N. J.) Hospital, where he died April 5, aged 67, of acute nephritis.

Pesquera, Gilberto Severiano, Saratoga Springs, N. Y.; born in San Juan, P. R., in 1894; College of Physicians and Surgeons, Baltimore, 1915; member of the American Trudeau Society and the Association of Life Insurance Medical Directors of America; formerly assistant medical director, Metropolitan Life Insurance Company, New York City; veteran of World Wars I and II; from 1951 to 1953 served in the Army of the United States; associated with the Saratoga Hospital; died in Santurce, Puerto Rico, Feb. 26, aged 66, of recurrent coronary thrombosis.

Pierce, Nathaniel H., Atlanta, Ga.; Georgia College of Eclectic Medicine and Surgery, Atlanta, 1904; died March 27, aged 88, of cerebral vascular accident.

Porritt, Ross Joseph Ⓜ Pontiac, Mich.; Northwestern University Medical School, Chicago, 1935; member of the American Academy of Dermatology and Syphilology; fellow of the American College of Physicians; veteran of World War II; on the staffs of the Pontiac General and St. Joseph's Mercy hospitals; died April 16, aged 52, of coronary thrombosis.

Powers, John Judge Ⓜ Albany, N. Y.; Albany Medical College, 1935; interned at the Albany Hospital, where he served a residency; served a residency at the Mary McClellan Hospital, Cambridge; since 1952 health commissioner of Albany County; veteran of World War II; certified by the National Board of Medical Examiners; specialist certified by the American Board of Preventive Medicine; served on the faculty of his alma mater; associated with Albany and St. Peter's hospitals; died April 17, aged 50, of coronary sclerosis.

Putman, Lynn J., Fort Lauderdale, Fla.; University of Maryland School of Medicine, Baltimore, 1909; died in the Broward General Hospital April 3, aged 73, of leukemia.

Raber, Daniel Deronda, Bloomington, Ill.; Bennett Medical College, Chicago, 1908; past-president of the McLean County Medical Society; first vice-president of the McLean County Historical Society for 25 years; veteran of World War I; associated with the Brokaw Hospital in Normal, St. Joseph's Hospital, and the Mennonite Hospital, where he died April 3, aged 81, of cerebral vascular accident.

Ragan, David Yandell Ⓜ Cold Spring, Ky.; University of Louisville School of Medicine, 1920; associated with the Speers Memorial Hospital in Dayton and St. Luke Hospital of Campbell County in Fort Thomas; died April 13, aged 68, of uremia.

Rainer, James William Ⓜ Odessa, Texas; University of Texas Southwestern Medical School, Dallas, 1944; interned at the Parkland Hospital; a medical officer in the medical corps of the Naval Reserve; associated with the Medical Center Hospital; died April 13, aged 42, in a private plane crash.

Ramsdell, Edwin George Ⓜ White Plains, N. Y.; born in New York in 1886; Columbia University College of Physicians and Surgeons, New York City, 1908; member of the founders group of the American Board of Surgery; in 1936 member of the House of Delegates of the American Medical Association; member of the International Society of Surgery–American Branch and the American College of Gastroenterology; fellow of the American College of Surgeons; formerly on the faculty of his alma mater; past-president of the Westchester County Medical Society; served as president and treasurer of the American Goiter Association; since 1934 president of the Westchester County Board of Health; formerly health officer of White Plains; in 1915 went to the American Hospital in Neuilly, France, and during World War I was a major in the medical corps of the American Expeditionary Force in the St. Mihiel Argonne offensives; for his war services was made a Chevalier of the Legion of Honor and received the Croix de Guerre with Palm; a colonel in the Army Medical Reserve Corps, served as chief of staff of the Westchester County Civil Defense Organization, which he helped establish early in World War II, and for many years was a medical adviser to the Westchester Chapter of the American Red Cross; past-president of the Alumni Association of the College of Physicians and Surgeons and, at his death, a trustee of the Alumni Council; on Dec. 6, 1951, received Columbia University's Lion Award for "outstanding service to his country, community, and to his university"; chief of staff and member of the board of governors of the White Plains Hospital; consultant, New York Hospital–Weschester division, White Plains, Mount Vernon (N. Y.) Hospital, Peekskill (N. Y.) Hospital, and Lawrence Hospital, Bronxville, N. Y.; director of the County Trust Company; died April 12, aged 73, of adenocarcinoma of the liver.

Rhodes, William Heilman Ⓜ Enid, Okla.; Maryland Medical College, Baltimore, 1902; died in the Enid General Hospital April 8, aged 83, of arteriosclerotic heart disease.

Roberts, Frank Eugene, Charlton, Mass.; Boston University School of Medicine, 1902; formerly practiced in Boston; died April 7, aged 80, of cerebral hemorrhage.

Robinson, Lewis Byrne Ⓢ New York City; Columbia University College of Physicians and Surgeons, New York City, 1911; served on the faculty of his alma mater; veteran of World War I; a consulting dermatologist at Englewood (N. J.) Hospital and the Presbyterian Hospital; since 1915 member of the department of dermatology at the Vanderbilt Clinic; died in St. Luke's Hospital April 24, aged 74, of myocardial infarction.

Schaefer, Constantine Richard Ⓢ Indianapolis; Medical College of Indiana, Indianapolis, 1890; Columbia University College of Physicians and Surgeons, New York City, 1892; served as professor of therapeutics at the Indiana University School of Medicine; formerly associated with the Protestant Deaconess Hospital and member of the staff of the Indianapolis City Hospital; died April 13, aged 90, of rectal hemorrhage-probable cancer.

Schiller, Walter, Evanston, Ill.; born in Vienna, Austria, Dec. 3, 1887; Medizinische Fakultät der Universität, Vienna, Austria, 1912; director of laboratories of second gynecological klinik at the University of Vienna before coming to the United States; originator of the Schiller test for the detection of cancer of the uterus; specialist certified by the American Board of Pathology; founding fellow of the College of American Pathologists; member of the American Association of Pathologists and Bacteriologists, and American Society of Clinical Pathologists; honorary member of the Phi Lambda Kappa, Midwest Clinical Society, Mississippi Valley Medical Society, and the Austrian Gynecological Society; served as chief of the pathology department at the Cook County Hospital in Chicago, where he was director of laboratories; consultant pathologist at Columbus, Mary Thompson, and Cuneo hospitals in Chicago; at one time on the staff of the Women and Children's Hospital, in Chicago; formerly pathologist at the Jewish Memorial Hospital in New York City; in 1959 honored by the United States Section of the International College of Surgeons and was presented with a certificate of recognition of his outstanding work; died May 2, aged 72, of bronchopneumonia and paralysis agitans.

Schmitz, Herbert Eugene Ⓢ Chicago; born in Chicago Oct. 10, 1901; Loyola University School of Medicine, Chicago, 1927; professor and chairman of the department of obstetrics and gynecology of Stritch School of Medicine of Loyola University; member of the president's council, Loyola University; professor of gynecology at Cook County Graduate School of Medicine; vice-chairman of the Section on Obstetrics and Gynecology, American Medical Association, 1948-1949; president-elect, American College of Obstetricians and Gynecologists; served as treasurer of the American Academy of Obstetrics and Gynecology; vice-chairman of the board of governors of the Illinois Division of the American Cancer Society and in 1952 received its award for contributions leading to better diagnosis and more effective treatment of carcinoma of the cervix; member of the American Association of Obstetricians and Gynecologists, of which he was past-president, American Gynecological Society, Central Association of Obstetricians and Gynecologists, of which he was past-president, Radiological Society of North America, and the American Radium Society; past-president and secretary of the Chicago Gynecological Society; fellow and member of the board of governors of the American College of Surgeons, and member of the Chicago Credentials Committee; member of the board of governors of the Institute of Medicine of Chicago; specialist certified by the American Board of Obstetrics and Gynecology of which he was vice president; chief of staff, St. Vincent's Infant and Maternity Hospital; senior attending gynecologist at the Cook County Hospital; chief of staff of the Lewis Memorial Maternity Hospital; chairman of the department of obstetrics and gynecology, Mercy Hospital–Loyola University Clinics; director of the Institute of Radiation Therapy, Mercy Hospital, where he died April 17, aged 58, of massive cerebral hemorrhage.

Schuett, Albert John Ⓢ Dallas, Texas; Baylor University College of Medicine, Dallas, 1921; on the staffs of St. Paul Hospital and Baylor University Hospital, where he died April 7, aged 64, of acute myocardial infarction.

Shapiro, Nathaniel Joseph, Union City, N. J.; Eclectic Medical College of the City of New York, 1907; died in the North Hudson Hospital, Weehawken, April 14, aged 78, of myocardial infarction and diabetes mellitus.

Skinner, Durward Alto Ⓢ Newark, Ohio; Ohio State University College of Medicine, Columbus, 1927; member of the American Society of Ophthalmologic and Otolaryngologic Society and the American College of Allergists, of which he was elected vice-president; on the staff of the Newark Hospital; died March 30, aged 60, of carcinoma.

Smith, George W., Louisville, Ky.; Louisville (Ky.) Medical College, 1893; died April 18, aged 92, of cerebral hemorrhage.

Smith, L. Allen Ⓢ Los Angeles; Long Island College of Medicine, Brooklyn, 1946; interned at the Long Island College Hospital in Brooklyn; served a residency at the Veterans Administration Hospital in Dallas, Texas, and the Veterans Administration

Center in Los Angeles; formerly an officer in the medical corps, Army of the United States; certified by the National Board of Medical Examiners; on the staff of Cedars of Lebanon Hospital; shot and killed April 30, aged 37, when his home was burglarized.

Steffensen, Ellis H. ® Detroit; University of Michigan Medical School, Ann Arbor, 1940; interned at the Henry Ford Hospital, where he served a residency and was a member of the department of ophthalmology; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; veteran of World War II; died April 9, aged 47, of coronary occlusion.

Stimpson, Edward W., Bellingham, Wash.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1903; past-president of the Whatcom County Medical Society; affiliated with St. Luke's and St. Joseph's hospitals; died April 14, aged 85, of coronary arteriosclerosis.

Szur, Ralph James ® Bridgeport, Conn.; Magyar Kiralyi Pazmany Petrus Tudomanyegyetem Orvosi Fakultasa, Budapest, Hungary, 1943; served a residency at the Charlotte Hungerford Hospital in Torrington; on the staffs of St. Vincents and Bridgeport hospitals; died April 17, aged 48, of acute coronary thrombosis.

Tate, William Cummings, Banner Elk, N. C.; Tennessee Medical College, Knoxville, Tenn., 1908; past-president of the Banner Elk Bank; for many years president of the Edgar Tufts Memorial Association; fellow of the American College of Surgeons; for 45 years served as medical director of the Grace Hartley Memorial Hospital, where he died April 2, aged 74, of cerebral thrombosis.

Terry, John Banner, Warren, Ariz.; University of Arkansas School of Medicine, Little Rock, 1937; interned at Santa Rosa Hospital in San Antonio, Texas; veteran of World War II; served on the staff of the Copper Queen Hospital in Bisbee; died in the Veterans Administration Hospital, Long Beach, Calif., April 5, aged 46, of brain tumor.

Tierney, John Patrick, St. Johnsbury, Vt.; Baltimore Medical College, 1911; town physician and health officer; on the staffs of the Brightlook Hospital and St. Johnsbury Hospital, where he died March 28, aged 72, of coronary occlusion.

Tuynman, Peter Edward, Detroit; Creighton University School of Medicine, Omaha, 1944; interned at the Mount Carmel Mercy Hospital, where he served a residency and was a staff member; an officer in the medical corps, Army of the United States, from July, 1945, to June, 1947; an assistant Wayne County medical examiner; killed April 21, aged 41, in an automobile accident.

Viele, John Spiecher, Lieut., U. S. Navy, Pensacola, Fla.; New York Medical College, Flower and Fifth Avenue Hospitals, New York City, 1958; interned at the Naval Hospital in Charleston, S. C.; commissioned in the U. S. Navy in 1957; certified by the National Board of Medical Examiners; drowned in Pensacola Bay Feb. 6, aged 28, when a small boat in which he was riding overturned.

Wade, Robert Lavern, Coldwater, Mich.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; fellow of the American College of Surgeons; member of the Industrial Medical Association; on the staff of the Community Health Center; died April 16, aged 83, of pneumonia.

Walker, Alfred Edgar ® St. Paul; Bellevue Hospital Medical College, New York City, 1890; formerly practiced in Duluth, Minn., where he was on the staff of St. Mary's Hospital; died in St. Joseph's Hospital April 14, aged 97, of heart failure.

Webb, Granville Pearl, Burning Springs, Ky.; Louisville (Ky.) Medical College, 1905; died in the Good Samaritan Hospital, Lexington, April 7, aged 85.

Webb, Harold Brown, Camden, S. C.; Medical College of South Carolina, Charleston, 1927; immediate past-president of the Kershaw County Medical Society; veteran of World War II; industrial physician for the DuPont Company; on the courtesy staff of the Kershaw County Memorial Hospital, where he died April 11, aged 56, of Hodgkin's disease.

Weddle, Achilles A. ® Somerset, Ky.; Louisville and Hospital Medical College, 1908; member of the city council; once served as mayor of Hustonville; associated with the Somerset City Hospital, where he died April 12, aged 80, of papillary adenocarcinoma.

Whalen, Edward William ® Scranton, Pa.; Jefferson Medical College of Philadelphia, 1925; member of the American Academy of General Practice; served as chief of medicine at the State Hospital and on the staffs of St. Mary's and Mercy hospitals; died April 17, aged 60.

Wilson, Edward William ® San Leandro, Calif.; Stanford University School of Medicine, San Francisco, 1935; specialist certified by the American Board of Dermatology; member of the American Academy of Dermatology and Syphilology; served on the faculty of his alma mater; associated with the Providence East Oakland, Peralta, and Children's hospitals in Oakland; retired from the regular U. S. Navy July, 1940; died April 15, aged 50.

FOREIGN LETTERS

AUSTRIA

Carcinoma of the Eyelid.—A. Pillat of Vienna (*Mkurse ärztl. Fortbild.* 9:227-230, 1959) observed that carcinomas of the eyelid, when treated by intratumoral injections of ethylenediamine quinone, healed with the formation of a delicate, cosmetically satisfactory scar. In a series of 13 patients with this condition no relapse occurred during a follow-up period of two and one-half years. The first injection was usually made below and under the tumor, and subsequent injections were made into the tumor.

BRAZIL

Brazilian Trypanosomiasis.—Negmme and Schenone (*Rev. méd. Chile* 88:82, 1960) studied a series of 21,581 inhabitants of northern Chile for the presence of Trypanosoma cruzi. As the parasite was found in 8.4% of the blood samples taken, infestation might be present in about 100,000 of the total population of 1,200,000. When the complement-fixation test was used, a positive reaction was obtained in 15.3% of 14,902 tested persons. In most patients the condition is chronic, with few if any symptoms. The authors called attention to the recent finding of six premature infants with congenitally transmitted trypanosomiasis. Dogs and cats act as a reservoir of the infection. Primaquine is the treatment of choice. Chlortetracycline and cortisone aggravate the disease.

DENMARK

Bronchiectasis.—E. Husfeldt (*Acta chir. scandinav.* [supp.] 245:76, 1956) reported having operated on 86 patients with bronchiectasis, from 1943 to 1953. During the period 1943 to 1947, 31 patients had resections, and postoperative empyema developed in 11; 4 of them died from the empyema. Operations were performed on 70 patients during the years 1948 to 1953. Postoperative empyema developed in seven of these and none of them died. In the last three years there has been only one death, and it resulted from a pulmonary embolism. In the period 1948 to 1953 there were six deaths. When the patients were divided into two groups, those under 30 and those 30 years of age or over, it was found that in the first group (31 patients) there was one death or a case fatality rate of 3%, and in the second group (38 patients) there were five deaths, or 13%. About 70% of the patients had a good result from the operation and were either cured or much improved. Pneumonectomy and lobectomy are the treatment of choice. The operation should not be delayed and should be as radical as possible. Segmental resection is of limited value.

The author concluded that so-called primary or lobar bronchiectases caused by lung infections in the early childhood and occurring mostly in small and debilitated children suffering from malnutrition and vitamin deficiency is becoming rare in Denmark. The cases still seen are diagnosed earlier, and the patient is sent to the thoracic surgeons at an earlier stage of the disease. The type of patient seen 20 years ago who brought up several ounces of fetid sputum daily has almost disappeared. This confirms the belief that bronchiectasis is mainly an acquired rather than a congenital disease.

FINLAND

Solitary Pulmonary Tumors.—The solitary pulmonary tumor or coin lesion presents a serious problem to clinicians since it may signify either an extremely malignant or a benign condition. Peräsalo and Tala (*Acta chir. scandinav.* [supp.] 245:119-128, 1959) studied a series of 200 such lesions. Of these, 137 or 68.5% were malignant; 114 were bronchial carcinomas. The 63 benign tumors included 41 granulomas. Together, bronchial carcinomas and granulomas accounted for 155 or 77% of the total number of solitary lung tumors. It was impossible to distinguish positively between the malignant and benign tumors except by thoracotomy. Cytological examination of sputum led to the detection of malignant cells in 14% of the patients, and positive results were obtained with bronchoscopy in 17.5%. There were no deaths when the tumor was removed by limited resection (52 patients). There were eight deaths (4%) after lobectomy and pneumectomy. One patient died of metastasis without operation. The authors concluded that thoracotomy should be performed on any patient in whom the roentgenogram revealed a solitary noncalcified shadow.

FRANCE

Barbiturate Poisoning.—At the meeting of the Medical Society of the Hospitals of Paris, J. F. Monsallier reported the results of experimental studies on dogs in which he observed that the variations of the pH of the plasma acted on the distribution of barbiturates in the organism in the following man-

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The items in these letters are contributed by regular correspondents in the various foreign countries.

ner: respiratory acidosis caused accumulation of the barbiturates in the cells, but alkalosis in the plasma caused a diminution in the quantity of barbiturates in the cells, particularly in the nerve cells. Alkalization of the urine markedly increased the renal excretion of phenobarbital. This excretion, due to renal alkalization, was more significant than that provoked by polyuria. The author treated 75 patients, who had severe coma due to barbiturates, by alkalizing the plasma. This treatment shortened the duration of the coma. The author emphasized the futility and the danger of nervous stimulants which are given as an antidote for acute barbiturate poisoning. The danger consists of convulsive manifestations which aggravate the hypoxemia and cause irreversible brain damage.

Alpha-Chymotrypsin for Deafness.—J. Causse (*Ann. oto-laryng.*, Nov., 1959) used alpha-chymotrypsin, an enzyme obtained from the pancreas of heifers, in operations for deafness. Alpha-chymotrypsin has proteolytic properties and hydrolyzes the fibrinous formations that result from inflammation. It is used in ophthalmology for lens extractions. The author's series included 49 patients, 33 of whom had otosclerosis, 15 of whom required a tympanoplasty, and 1 of whom had a dry adhesive otitis media. The technique consisted in the instillation of a solution of 5 mg. of alpha-chymotrypsin in 10 cc. of serum. In order to prevent inactivation of the enzyme, fresh solutions should be used. Even small traces of alcohol on the instruments which are used for instillation should be avoided, and the solution should not be overheated. By using this enzyme, the fibrous formations became soft and it was possible to liberate and mobilize the stapes. No labyrinthine complication occurred and no harmful effect on the articulation of the ossicles was noted. Although immediate functional improvement was observed, whether this could be maintained has not yet been determined.

Steroids for Lipoid Nephrosis.—R. Pachioli and co-workers (*Arch. franç. pediat.*, no. 6, 1959) reported the results of treatment in 41 children with lipoid nephrosis. The administration of steroids was [illegible]d in cycles, the first of which lasted from [illegible] 12 days and the next from 3 to 6 days. The intervals between the treatments varied from 4 to 10 days, and the treatment was given for a total of at least six months until the condition of the patient, from the urinary and humoral point of view, returned to normal. ACTH, which acts rapidly, was given intramuscularly in daily doses of 5 to 8 units per kilogram of body weight, or intravenously in daily doses of 2 units per kilogram of body weight. Prednisone and prednisolone, both of which act less rapidly than ACTH, were given by mouth in daily doses of 2 to 3 mg. per kilogram of body weight.

Dexamethasone in daily doses of 0.2 mg. per kilogram of body weight gave rapid results with a minimum of water and salt retention. No glycosuria, hypertension, or gastric or psychic disturbance resulted from this prolonged treatment. Obesity was frequently noted, but it disappeared within two months after treatment was stopped. Treatment resulted in remissions of long duration, interpreted by the authors as cures in 80 to 85% of the patients.

Dexamethasone for Asthma.—J. Turiaf and coworkers (*Thérapie*, no. 6, 1959) used dexamethasone in the treatment of 30 patients who had asthma. The dosage for patients with status asthmaticus was 6 to 8 mg. in 24 hours, which was five to seven times less than that of deltacortisone. The effect in five of six patients thus treated was slightly superior to that obtained with ACTH or deltacortisone. In four patients with persistent dyspnea who had not previously been treated with corticoids, the administration of dexamethasone in doses of 3 to 4 mg., gradually diminishing the daily doses to 1 or 2 mg., caused rapid improvement. Among the other asthmatic patients with persistent dyspnea, the disease was perfectly controlled by deltacortisone in 14. Comparable results were obtained with dexamethasone in 10, inferior results in 2, and superior results in 2.

The advantage of dexamethasone consisted in the relatively low dosage and diminution of undesirable side-effects. This product was 7 times more active than deltacortisone, 28 times more active than hydrocortisone, and 33 times more active than cortisone. This treatment necessitated, as with other corticoids, a strict sodium-free diet and the administration of potassium. It may provoke such complications as osteoporosis and osteomalacia. There are risks of hemorrhage, perforation of the digestive tract, and also of an inhibitory influence on the adrenal cortex.

GERMANY

Age and Sex Distribution of Diabetes.—At the sixth symposium of the German Society for Endocrinology at Kiel in 1959, Hevelke of Leipzig stated that, while at the beginning of the century the sex distribution of diabetes was 69 men to 31 women, by 1939 it had shifted to a ratio of 50:50, and by 1958 it had further shifted to a ratio of 36:64. In other words it had virtually become reversed since 1900. The higher mortality in women is not only relative, owing to the greater number of women affected, but it is absolute. This rate is 5.12% in men and 7.09% in women. Among those in whom the disease develops before the 45th year of life men predominate, but in higher age groups women predominate. The increasing life span may be expected to be associated with a further increase of diabetes in women. An interrelationship between diabetic manifestations and the activity of the gonads is also inferred from the fact that, among women with newly discovered cases of diabetes, there are five or six times as many who are at the period of onset of menopause as of those who have not yet reached, or who have passed, this period. Other endocrine disorders occurring frequently at this time are hypertension, obesity, and hypercorticism.

Surgical Treatment of Portal Hypertension.—A Gütgemann and co-workers (*Deutsche med. Wchnschr.* 84:1505-1508, 1959) stated that the previously hopeless prognosis of portal hypertension has been improved by surgical treatment. In a series of 201 patients, 83% had an intrahepatic block and 17% an extrahepatic block. The mortality risk of a shunt operation was found to be below 10% in patients with compensated liver function. Since the case fatality from a first severe varicose bleeding is about 30%, portocaval anastomosis should be decided on as early as possible. The absolute indication is massive hemorrhage. In other patients operation should be considered only when mild esophageal or gastric bleeding or x-ray evidence of varices are present.

Prerequisite of the operation is good conservative pretreatment because the operation puts a severe strain on the liver. Patients with scarred livers and inactive compensated cirrhosis in whom hepatic function is well maintained, and those with the mixed forms between scarred liver and cirrhosis, are suitable for operation. Relative indications are bleeding varices with ascites which can be controlled by conservative measures and multiple hemorrhages with mild decompensation. Contraindications are progressive and active cirrhosis, decompensated cirrhosis with marked ascites, and impairment of hepatic function.

Liver Damage from Oral Treatment of Diabetes.—Illig and co-workers of Giessen (*München. med. Wchnschr.* 101:2121, 1959) stated that their observation of jaundice in diabetic patients treated with sulfonylurea derivatives led to the examination of ambulant diabetic patients for possible hepatic impairment. The patients were divided into a carbutamide-treated group, a tolbutamide-treated group, and a control group treated with diet, insulin, or both. An increase in the incidence of liver damage corresponding to duration of treatment was found in all groups. A significant increase in liver damage was seen in the first group, but there was no notable difference between the other two groups. The authors concluded that tolbutamide was preferable for the oral treatment of diabetes.

Prostatectomy.—Boeminghaus and Klosterhalfen (*Ztschr. Urol.* 52:485, 1959) reported a series of 1,000 persons with retropubic extravesical prostatectomies in whom operability mainly depended on the functional reserve of the heart and the efficiency of the kidneys. Only the urologist can decide on the indication for prostatectomy, but the internist's opinion of cardiac functional reserve is important. The difficulty in making the decision may be seen from the fact that in 60% of the deaths cardiac and circulatory failure were responsible. With regard to the efficiency of the renal parenchyma, Volhard's test and the estimation of the nonprotein nitrogen level are still considered important, and the phenol red test is recommended.

In doubtful cases the patient also should have a word in the decision as to whether to operate or not. Age is not an important factor, although most deaths were in persons who were 70 to 75 years of age. Hypertension is no contraindication. Hypertensive patients usually had an uneventful postoperative course, but in those with chronic hypertension episodes of postoperative apoplexy have occurred. Diabetes is no contraindication, but careful control of the sugar balance and careful postoperative supervision of circulation are required. Wound treatment and wound healing do not present complications in the diabetic patient. General mortality in this series was 2.5%, with cardiac failure ranking highest as a cause of death followed by pulmonary embolism and uremia. The authors attributed the comparatively low number of pulmonary emboli to such preventive measures as raised position of the legs after the operation, bandaging of the lower legs, and active exercises as soon as possible. Anticoagulants are not used for prophylaxis after prostatectomy.

Penicillin-Resistant Gonococci?—H. Gertler (*Ztschr. ärztl. Fortbild* 53:169-172, 1959) stated that all patients whose gonorrhea was treated with penicillin between 1953 and 1957 were checked for relapses. The difference between relapses in ambulant and hospital patients was significant. In a great number of the ambulant patients apparent relapses were in fact reinfections (5.2% in 1953; 4.3% in 1954; 2.6% in 1955; 2.7% in 1956; and 2.8% in 1957). Other causes of apparent relapses in the group included concomitant balanitis and condylomas in men and chronic adnexal processes or chronic bartholinitis in women. On the other hand in the hospital-treated patients who had had 400,000 to 600,000 units of penicillin G, there were only three relapses in 1953 (1.2%), only one each (0.3%) in 1954 and 1955, and no relapses since then. From the low number of relapses in hospital-treated patients it is concluded that gonococci have not yet lost their sensitivity to penicillin, and the emergence of resistance is hardly to be expected in the future.

Kallikrein Inhibitor.—Werle and Appel of Munich University (*Ztschr. Naturforsch.* 14b:385-392, 1959) studied the occurrence of the kallikrein inactivator in 23 mammals (including man). Large amounts of kallikrein inactivator were found in the organs of several ruminant animals. The blood serum of all species investigated, including cold-blooded animals, contained kallikrein inactivator and a trypsin inhibitor. Organic extracts containing kallikrein inactivator also inhibited trypsin. The relation of kallikrein inactivator to trypsin inhibitor was constant within certain limits. When the kallikrein inactivator from bovine liver was purified to standard, the trypsin inhibitory property was maintained. The fact that the inhibitor was capable of acting on both kallikrein and trypsin suggested a similarity in the structure of the active centers of the two molecules.

Plasmocytoma and Macroglobulinemia.—U. Kanzow of Cologne University (*Medizinische* pp. 1352-1358 & 1361, 1959) studied a series of 51 patients with plasmocytoma and 17 with macroglobulinemia. Skeletal changes were more frequent in patients with plasmocytoma, and roentgenographic evidence showed osteolytic foci in about 80% of these patients. Occasionally such foci also were seen in patients with macroglobulinemia. Although loss of efficiency, loss of weight, anemia, increased sedimentation rate, and hyperproteinemia were observed almost equally in patients with both diseases, macroglobulinemia was marked by greater involvement of the liver and spleen. Abnormal findings were observed in the marrow in almost all patients with both diseases, and in those with macroglobulinemia the reticulum cells termed "lymphoid" were always found. These occasionally showed a plasma cellular differentiation, and in this disease also, the plasma cells and tissue mast cells were increased.

A remarkable finding was the frequence of albuminuria with Bence Jones proteinuria in patients with macroglobulinemia. An increase in nonprotein nitrogen and disturbances of renal function were seen in patients with plasmocytoma but not in those with macroglobulinemia. Paramyloid deposits were found in about 10% of the patients with plasmocytoma but never in those with macroglobulinemia. True amyloid deposits were seen in about 10% of those with macroglobulinemia, however. In 35 patients with plasmocytoma the average duration of survival after the occurrence of suggestive symptoms was 27 months (8 months after establishing the diagnosis), while the life expectancy in those with macroglobulinemia, except for those with an acute course, was longer. Electrophoresis showed no characteristic changes in 6 of 47 patients with plasmocytoma. In 25 there was a γ-paraproteinemia. In patients with paraproteinemia the serum protein level averaged 8.83 Gm. per 100 ml. or somewhat lower than in patients with plasmocytoma without paraproteinemia (9.77 Gm. per 100 ml.). The same increase of serum protein level was seen in patients with macroglobulinemia.

Postabsorptive Hypoglycemia.—Bahner and Schwarz of Heidelberg University (*Ärztl. Wchnschr.* 14:611-617, 1959) stated that three phases are differentiated in patients with hypoglycemia: (1) autonomic symptoms, (2) spasm, and (3) the so-called hypoglycemic crisis. In postabsorptive hypoglycemia, usually only the symptoms of the first phase are observed. These occur two to four hours after the person has eaten a meal rich in carbohydrates. The authors observed the following symptoms in this order of frequency: fatigue with heaviness of limbs, restlessness with trembling, palpitations, sweating, nausea with retching, gastric pressure, insomnia, giddiness, tendency to collapse, headache, and hunger. Since hunger is the least frequent symptom, the condition is often not understood, and a diagnosis of hyperthyroidism, autonomic imbalance, hypotension, circulatory disturbance, or tetany may be made.

Further characteristics of postabsorptive hypoglycemia are that the patient is inattentive, lacking in contact, and doing his work mechanically, which may be dangerous when he is driving a car or operating any heavy machinery. Postabsorptive hypoglycemia normally affects only the obese, since obesity is usually the result of excessive carbohydrate intake. If the epigastric symptoms of postabsorptive hypoglycemia are interpreted as due to a disease of the epigastric organs and a high carbohydrate diet is prescribed, the symptoms may be aggravated. Postabsorptive hypoglycemia in patients who have had a gastric resection is improved when the carbohydrate content of the diet is reduced. A tendency to hypoglycemia can be proved by a glucose tolerance test which shows a rapid decline of the blood sugar level.

When typical symptoms occur two to four hours after a carbohydrate-rich meal, the diagnosis can be regarded as established even if no blood sugar examination is made. Postabsorptive hypoglycemia may be caused by (1) massive carbohydrates absorption which gives rise to reactive release of insulin followed by hypoglycemia, (2) an increase in insulin sensitivity owing to suppression of secretion by the anterior pituitary and (3) physical exercise. Since foods rich in carbohydrates are cheap, keep well, and are easily prepared, they usually form the bulk of mass meals. Postabsorptive hypoglycemia is therefore likely to affect workers who do no heavy work. Treatment consists of taking more protein and less carbohydrate.

INDIA

Neurological Manifestations in Kwashiorkor.—P. M. Udani (*Indian J. Child Health* 9:103 [Feb.] 1960) reported the neurological and psychiatric manifestations seen by him in 15 patients with kwashiorkor. These patients were between 6 months and 4 years of age. All had typical kwashiorkor with marked mental changes, varying degrees of edema, dermatitis, and stunting of growth. Three had a positive tuberculin test result. Nine had vitamin A deficiency, and five had deficiency of the vitamin B complex. All had moderate anemia, not severe enough, however, to account for the neurological changes. The spinal fluid in patients with gross neurological signs was normal except in one who had increased protein levels and elevated red and white blood cell counts. This patient was found later to have a subdural hematoma. The neurological examination revealed mental changes and motor involvement.

Twelve patients had pain, irritability, a whining cry, and sometimes apathy and drowsiness. In two of these the findings simulated those of hepatic coma and the patients died. Postmortem liver biopsy showed only fatty changes in the liver. One patient had terminal convulsions. The blood sugar level immediately after death was zero. The patient, therefore, died of severe hypoglycemia. Dulness and apathy were marked in the older children, but these improved dramatically after a few days of treatment. Two children showed such behavior disturbances as biting and hair pulling.

The motor involvement was observed to be either a lower or an upper motor neuron type of lesion. The commonest was the lower motor neuron type, described as nutritional amyotonia. These children had hypotonia with absent deep reflexes which returned in most instances after four to six weeks of treatment. Muscular weakness, hypotonia, and loss of deep tendon reflexes occurred without loss of sensation. The absent deep reflexes were not correlated with the severity of the muscular changes. The clinical findings in these patients resembled those of amyotonia congenita. The children had an ataxic gait, and their mode of getting up from the bed sometimes resembled that seen in patients with muscular dystrophy. Two patients had upper motor neuron lesions (nutritional myelopathy). One of them recovered after treatment. Three had a peculiar syndrome, called recovery encephalopathy, seen while they were under treatment. Coarse tremors, seen better in the upper extremities and most marked in the hands, were the characteristic features. They resembled the pill-rolling movements of persons with paralysis agitans. One patient also had tremors in the tongue and all three showed slight tremors in the lower limbs. One of these children had hypotonia, but the tone was increased in the other two.

The deep reflexes were exaggerated. No patient showed significant anemia. One of them improved after treatment. Disturbances of the autonomic nervous system, in the form of cold extremities in the absence of circulatory failure, were common. Six had flushing of the face and soles of the feet. Two patients had painless perforating ulcers on the feet and both died; such ulcers are believed to be a bad prognostic sign. The exact cause of these lesions was probably severe malnutrition. Deficiency of the vitamin B complex may be a contributory factor, but most of the children recovered without supplementary vitamins. Potassium deficiency may be responsible for the hypotonia and loss of reflexes but estimations of the blood potassium level, made in a few instances, were within normal limits. Viral encephalitis and toxic encephalopathy should, however, be excluded. Brain damage may occur in patients with kwashiorkor, as was seen in one with severe mental changes who at autopsy was found to have cystic areas in both occipital lobes and sclerosis in the cerebral cortex.

PORTUGAL

Griseofulvin.—After 10 months experience with griseofulvin J. Esteves and H. Neves (*J. Medico* 41:253) obtained a cure of tinea capitis in 22 children treated with 0.5 to 1 Gm. of the new drug daily for three to five weeks. In four other patients interruption of treatment was followed by new lesions which were regarded as reinfections. In seven adults who had chronic forms of tinea with multiple localizations cure was obtained after three to six weeks of treatment with 1 to 2 Gm. of the drug daily. Superficial lesions tended to heal after five or six months of treatment with 1 to 2 Gm. daily, but destructive lesions were more resistant to the antibiotic. In the glabrous skin there was clearing or disappearance of lesions after four to six weeks of treatment with 1 to 3 Gm. of the drug daily, but continuous treatment, even for four months, did not prevent constant relapses when the treatment was interrupted.

SWEDEN

Intermittent Pressure for Varicose Ulcers.—Dr. S. Rastgeldi (*Svenska Läk-sällsk. förhandl.*, Feb. 19, 1960) estimated that in Sweden alone there are about 80,000 persons who suffer from post-thrombotic relapsing leg ulcers reflecting varicose degeneration of the tissues. As it would take far too long a time to teach each patient separately the principles and technique of the elaborate system of intermittent pressure-treatment he advocates, Rastgeldi grouped his patients in large classes for collective instruction. Often the first reaction to this treatment is extension of an ulcer, due to the sloughing off of its necrotic margins, and an increased discharge of fluid from it, with itching. Answers to a questionnaire addressed to 100 patients who had undergone treatment listed no recurrence of thrombosis but did list various other sequelae such as increased diuresis in 30 to 35%, giddiness and general discomfort in 20 to 25%, and pain in the lower leg in 35 to 40%. To gauge the value of this treatment, the first 100 patients had no supplementary treatment except use of local anesthetics, for the relief of itching and sweating, and washing of the sore with an antiseptic. This austerity was subsequently relaxed so as to give the patient the benefit of rest and confinement to bed from time to time as a supplement or as an alternative to intermittent pressure. Rastgeldi deplored the laziness of the patients who failed to take the necessary precautions when not urged to do so by pain, nightly cramp, sweating, itching, and sense of heaviness in the legs.

Surgical Treatment of Ulcerative Colitis.—Dr. R. Lagercrantz and co-workers (*Svenska Läk-sällsk. förhandl.*, Feb. 19, 1960) found that late prognosis for the medical treatment of ulcerative colitis in childhood is unsatisfactory. Of 137 patients followed up for more than three years after the onset of colitis 20 had died. The cause of death in 18 of these was the colitis or its sequelae. Of 25 patients given conservative treatment and followed up for over 11 years, 8 had developed cancer of the colon. On the other hand, all the 17 patients operated on made a surprisingly rapid recovery and their general condition had greatly improved on discharge from hospital two to four weeks later. Hence it was advised that most patients with ulcerative colitis in childhood should be subjected to colectomy and ileostomy. When the rectum shows serious disease it should be extirpated either at the same time or later.

UNITED KINGDOM

A Case of Negligence.—A physician was censured by the London Executive Committee of the National Health Service and fined $60. The wife of a patient told the committee that the doctor first visited her 53-year-old husband on a Thursday. She asked him to come again on the following Monday, and at this time his visit lasted five minutes. She said that he seemed to be under the impression that he had prescribed tablets on his first visit when in fact he had not done so. Her husband's condition became much worse so she asked the physician to visit him on Wednesday. He took her husband's temperature and examined him with a stethoscope while he had a cigaret in his mouth, as had been the case on each of his earlier visits. The patient grew worse, and in the early hours of the morning his wife telephoned the doctor, who then sent an ambulance which took her husband to the hospital. He died the next morning. The committee found that the doctor did not diagnose pneumonia until his third visit and on two occasions examined the patient with a stethoscope applied over his pajamas. It concluded that the doctor showed lack of care in his treatment.

Glucose Tolerance and Uterine Bleeding.—Investigations were made by F. Benjamin (*Brit. M. J.* 1:1243, 1960) to determine the diagnostic value of glucose-tolerance studies in patients with abnormal uterine bleeding of benign and malignant origin. The results were correlated in each case with the histological findings in the endometrium. At first, patients with carcinoma of the body of the uterus were investigated and compared with control subjects in the same age groups. This was essential because it is known that age has an important bearing on glucose tolerance. The study was then extended to all patients with abnormal uterine bleeding, particularly those with benign glandular hyperplasia of the endometrium. Of the patients with cancer of the endometrium 52% showed impaired glucose tolerance, while only 22% in the control group showed such impairment, a significant difference. The incidence of impaired glucose tolerance in patients with proved benign glandular hyperplasia was 84%, which was much greater than that in the control groups and that of patients with cancer of the endometrium. The finding of this common factor of disturbed glucose tolerance lends weight to the suggestion that benign glandular hyperplasia and endometrial cancer are related. The association of the two conditions has frequently been reported. Excessive or prolonged estrogen activity has been suggested as a factor causing endometrial hyperplasia and its progression to carcinoma. Benjamin, however, believed that an aberration in carbohydrate metabolism occurs and that, just as diabetes predisposes to certain infections, this may render the patient with benign glandular hyperplasia more likely to develop carcinoma.

Protein-Binding Sulfonamides.—Recently there has been much interest in new sulfonamides that produce a persistently high blood level with a single daily dose and that give blood concentrations comparable with those produced by the established regimen of six hourly doses of the standard sulfonamides. Though in vitro these new drugs had similar antibacterial activity to sulfadiazine, some of the results of clinical trials were disappointing. In the hope of explaining these results, Newbould and Kilpatrick (*Lancet* 1:887, 1960) examined the protein-binding properties of three of the long-acting sulfonamides—sulfaphenylpyrazole, sulfamethoxypyridazine, and sulfachloropyridazine—and the effect of any such binding on their persistence in the blood and their penetration into the cerebrospinal fluid. The degree of attachment of sulfonamide to protein was measured by dialysing human plasma, to which sulfonamide had been added, against phosphate buffers.

The authors found that the new long-acting sulfonamides are more extensively bound to plasma protein than are the older sulfonamides, such as sulfadiazine and sulfamethazine. This extensive protein-binding leads to lower diffusible concentrations in the plasma and therefore to lower concentrations in compartments such as the spinal fluid. The antibacterial activity of a sulfonamide depends on the diffisible concentration of active drug, which has no such activity when it is protein-bound. Acetylation rates also depend on the concentration of diffusible drug, and thus sulfonamides that are highly protein-bound are only slowly acetylated. On the other hand, the rate of renal excretion does not depend solely on protein-binding, since highly bound compounds such as sulfachloropyridazine are rapidly eliminated in the urine.

Higher total plasma concentrations are required with these newer sulfonamides than with the older ones to produce similar diffusible drug concentrations and a similar therapeutic effect. The protein-binding could explain some of the disappointing results of clinical trials with the new sulfonamides, which penetrate poorly into the spinal fluid. The generally recommended doses of the new sulfonamides were chosen by the manufacturers to give total plasma concentrations similar to those considered adequate for therapy with sulfadiazine and sulfamethazine. If such doses are used, lower tissue concentrations will result and the antibacterial activity will be less. The results of Newbould and Kilpatrick suggest that the therapeutic value of the new sulfonamides does not surpass that of the older compounds. Any increase in dose to raise the concentration of unbound drug in the plasma may increase the possibility of toxic effects.

New Fellows of the Royal Society.—Twenty-five new fellows have been elected to the Royal Society; four of them are medical men, and a number are those whose investigations have advanced medical science. J. N. Davidson, professor of biochemistry, Glasgow University, was elected because of his work on the chemistry of the nucleic acids. He demonstrated the synthesis of desoxyribonucleic acid in living cells. Sir Stewart Duke-Elder, another new fellow, is an opththalmic surgeon and director of research at the London University Institute of Ophthalmology. He is the author of "Textbook of Ophthalmology" and has made contributions on the intraocular circulation and glaucoma. Dr. P. A. Gorer, reader in experimental pathology at Guy's Hospital Medical School, London, received the fellowship in recognition of his research on immunology and tissue transplantation, including antibody reaction to transplanted malignant cells, and their relation to the genetic constitution of donor and recipient. Sir George Pickering, regius professor of medicine, Oxford, was elected for his research on hypertension, which he has found to be inherited as a graded character.

Some of the nonmedical fellows who have been working in fields related to medicine are Dr. D. G. Evans, director of the Medical Research Council's Biological Standards Control Laboratory, London, who worked on the pathogenesis and prophylaxis of anaerobic wound infection and whooping cough; Dr. H. E. Huxley, of the department of biophysics, University of London, honored for his research on the structure of muscle and the mechanism of muscular contraction; Dr. J. C. Kendrew, deputy director of the Medical Research Council's Unit for Molecular Biology, University of Cambridge, noted for his investigations on the x-ray diffraction examination of myoglobin; and Dr. E. N. Willmer, of the department of physiology, University of Cambridge, who was elected to the fellowship for his work on color vision and the growth and metamorphosis of cells.

General Practitioner Research Group.—The General Practitioner Research Group was formed in 1959 to undertake therapeutic trials in general practice. It now has over 60 members distributed throughout the country. David Wheatley (*Practitioner* 184:500, 1960) pointed out that, although rigidly controlled trials cannot always be made in general practice, the clinical impressions of a number of experienced practitioners may be of great value. Drug trials in general practice are becoming increasingly necessary because such illnesses as the common cold and fibrositis are treated exclusively by the general practitioner and are seldom, if ever, seen in hospitals.

There are also the practical aspects of therapy under home conditions as compared with hospital conditions. A patient in hospital will take almost anything, since he usually believes that once he leaves hospital he will be cured and will no longer have to continue treatment. At home, however, such seemingly unimportant factors as size and number of tablets, frequency of dosage, and flavor of mixtures may determine whether or not a given regimen will be followed. Side-effects which may appear unimportant in hospital may so affect a patient going about his ordinary work as to preclude use of the drugs concerned in general practice. Since its inception the group has undertaken 19 major clinical trials. These have included the trial of a nonbarbituric hypnotic, of an antiviral agent, of a long-acting coronary vasodilator, of a new antibiotic, and of a new remedy for premenstrual syndrome.

CORRESPONDENCE

NURSE ANESTHETISTS

To the Editor:—I desire to express my approval of the letter by Holzer in THE JOURNAL, April 9, page 1678, on the subject of nurse anesthetists. I agree that it is doubtful that it would be desirable to have all anesthetics administered by physicians. It probably would not be safer and would certainly be more expensive for the patient or the hospital or both.

Until my retirement four years ago, I was the director of the medical and surgical department of a large public hospital (7,500 beds), a position I held for 36 years. The surgical staff consisted of visiting surgeons and one or two full-time general surgeons. For the last 10 years of my tenure, the surgical staff was largely from the staff and faculty of a university school of medicine and hospital. During all of those years anesthesia was a serious problem, until about 1945, when the hospital began to employ full-time trained nurse anesthetists. Since that time, a corps of nurse anesthetists has been maintained at the hospital and has given complete satisfaction to the surgeons, patients, and hospital administration. I cannot recall a single death due to anesthesia, although one may have occurred. These competent nurse anesthetists maintain a 24-hour emergency schedule seven days a week. Occasionally, a physician anesthesiologist was secured when an especially difficult and long thoracic operation was anticipated.

I also agree with Dr. Holzer in not regarding the nurse anesthetist as only a stopgap until enough physician anesthetists are available to meet the needs. I am convinced that the nurse anesthetist has a permanent and essential place on the hospital team. In addition to her ability to develop competence with proper training, her psychological rapport with a great many patients, preoperatively, often creates confidence and a lessening of emotional tension in the patient. With Dr. Holzer, I beg teaching hospitals to restore the abandoned programs and to institute new ones where they do not now exist so that all hospitals will be able to provide an excellent anesthesia service.

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To the Editor:—In THE JOURNAL, April 9, page 1678, Charles E. Holzer Jr., M.D., says that nurse anesthetists "can provide a service comparable to that given by the best physician anesthetist and better than the average." He supports this statement with figures from his own hospital showing one death in 31,949 patients given anesthetics between 1950-1959 for surgery. By itself, this figure supports nothing because Dr. Holzer does not tell us how many patients died in the operating room and in the first 24 hours after surgery. The difficulty of separating operating-room deaths into those attributable to anesthesia and those not attributable to anesthesia has been well documented by the Philadelphia Anesthesia Study Commission and most recently by Vincent J. Collins, M.D., in a paper entitled "Fatalities in Anesthesia and Surgery" in THE JOURNAL, Feb. 6, page 549.

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To the Editor:—I would like to comment on Dr. Holzer's letter to the editor (*J. A. M. A.* 172:1678 [April 9] 1960). One must agree with the criticism of the paper by Cull (*J. A. M. A.* 172:416 [Jan. 30] 1960) pertaining to the reduction in deaths from maternal anesthesia at the MacDonald House in Cleveland between 1945 and 1956. Two possible variables influenced the results, namely, the increase in the use of conduction anesthesia and the increase in the participation of physician anesthesiologists. Although we cannot demonstrate from the data presented the relative contributions of these two factors, we must recognize that the use of conduction anesthesia grows concomitantly with the availability of personnel who can administer it safely. It would seem likely to those associated with anesthesiology departments that anesthesiologists at the MacDonald House have contributed to both of the variables.

Dr. Holzer operates at the Holzer Hospital, Gallipolis, Ohio. This is a 130-bed hospital which the Joint Commission on Accreditation of Hospitals has not approved for either intern or resident training. (*J. Am. Hosp. Assoc.* 33:162 [Aug. 1, pt. 2] 1959). There is on the staff of the hospital no physician who has been certified by the American Board of Anesthesiologists nor any who is a member of the American Society of Anesthesiologists (Directory of Members, Jan., 1960). Working from these environs, Dr. Holzer has outlined for THE JOURNAL the "ideal situation" for hospital anesthesia coverage. He states that "Anesthesiology is in itself . . . a technical discipline." That this is not consistent with the stand of the American Medical Association is indicated by a resolution of the House of Delegates passed in 1950 (*J. A. M. A.* 143:1080 [July 22] 1950) which reads, in part, as follows. "Resolved, That the American Medical Association recognizes the practice of anesthesiology, pathology, physical medicine and roentgenology as the practice of medicine."

Dr. Holzer cites the experience with anesthesia at the Holzer Hospital from 1950 to 1959 inclusive. Among 31,949 patients given anesthetics for surgical procedures and 8,484 patients given them for obstetric deliveries there was one death attributable to anesthesia. This amounts to an incidence of 0.25 deaths per 10,000 patients (1 in 40,433). In a review of 1,024 postoperative deaths in 20 hospitals in Baltimore, the incidence was 4 deaths per 10,000 patients, or 16 times as many (Phillips and others: Baltimore Anesthesia Study Committee, *J. A. M. A.*, to be published). Beecher and Todd (*Am. Surg.* 140:2 [July] 1954), in a survey of over 500,000 patients to whom anesthetics were administered in 10 universities, reported an incidence of 6.3 deaths per 10,000 anesthesias, or 25 times as many as in the Holzer Hospital. One might wonder whether the records of the role of anesthesia in postoperative deaths might be influenced by the ability of the reviewer to recognize the influence of anesthesia when a mishap does occur.

It seems that Dr. Holzer has not presented convincing evidence that the increasing use of physician anesthesiologists, which will lead to a smaller number of nurse anesthetists, will cause a decline in the average quality of anesthesiology throughout the country.

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ROOMING IN

To the Editor:—The article in The Journal, Oct. 24, 1959, page 1072, on the control of staphylococcic infections in a maternity unit, by Farrer and others, made pleasant reading. We have been watching for such an article for five years, and so far as we know it is the first on this subject which has emphasized the part played by staff in conveying infection.

For the past five years "rooming in" has been compulsory in the maternity section of the Royal Newcastle hospital. Our notion of rooming in is that the mother should take complete care of the baby from the time of birth to discharge, whether in a room or a ward. We apply this idea even to premature babies whose weight at birth is around 1,000 Gm. (2.2 lb.). As we have a follow-up clinic we are able to examine our patients after they leave hospital. In the period under review we have had no outbreaks of nursery infection and the infection rate has remained consistently low. It is difficult to quote exact figures, for standards vary, but a record of all infections that occur in our hospital, even mild "sticky eyes," is made on a large graph in the nursery each week, and the figure remains satisfactorily low.

Perhaps the most interesting result of the program has been the low figure for breast abscesses. About 90% of the babies are breast fed when they leave the hospital. Some 15 to 20% give up the breast feeding soon after leaving hospital. A nine-months follow-up study shows that the breast abscess rate has remained around 0.3%.

In the children's wards we encourage the parents to stay with their children as much as possible and to provide as much nontechnical nursing care as possible. All other visitors are banned. Our surgeons believe that they are mainly responsible for infections in elective surgery. Our whole staff has been reeducated to a belief in aseptic techniques.

We have not had occasion to publish anything on this subject, for our figures seem to be improving in most areas of patient care in respect to cross-infection and there is nothing spectacular in having things go well. We hope the results recorded in this article receive the attention they merit.

The following is a list of the rooming-in procedures adopted in this hospital.

Group A.—The mother is responsible for the entire care of her baby. This includes care required at night. All other attendants are excluded.

Group C.—Babies grouped in this class are babies that require specialized attention, e. g., difficult deliveries and premature babies, or babies whose mothers are unable to care for them because of their own condition, e. g., severe toxemia and cesarian section. As soon as the condition of either baby or mother is satisfactory, the baby is regrouped into class A.

Group D.—This class includes babies for adoption or very small babies who must be cared for by the nursing staff.

Class A and C babies are never handled by the medical or nursing staff with bare hands. In group D unnecessary handling of babies by the staff is discouraged.

Delivery Room Technique.—At delivery the initial treatment required for the baby is carried out by the nurse or doctor while they are still gowned and gloved. Provided the condition of the baby at delivery is satisfactory, the baby is inspected for abnormalities by the accoucheuse before it is removed from the delivery bed. It is weighed; scales are screwed to a trolley so that they are portable and a paper drape is placed on the tray of the scales before each baby is weighed. The eyes receive no attention at delivery. Babies are not sucked out as a routine procedure. The cord is tied twice, at the base and one inch from the base by the accoucheuse; no dressing or antiseptic is applied. Babies are not bathed after delivery; oil is never used in the unit.

Bathing Procedure.—A mother who has had a normal delivery is allowed to ambulate 20 hours after delivery if she is fully rested. When she feels capable of doing so, she is allowed to bathe her baby. This initial bathing of the baby will not take place until the day after delivery or even later. It depends on how the mother feels. The mother sits to bathe her baby. The baby is bathed on a low table (height 27 in., width 20 in., and length 34 in.). The table is covered with a drawsheet which is in turn covered with brown paper. The bathing is done from a washbasin placed on the table on the left-hand side. This basin is filled with water by the mother, and the temperature is tested by her.

Until the mother is competent the bathing is supervised by a nurse, who demonstrates the procedure on a rubber doll. The nurse has the same equipment to use as the mother; i. e., the doll has its own cot, clothes, etc. One nurse cannot demonstrate to more than two mothers at one time. A bathing so described usually takes about 20 minutes.

At the first bathing the baby is measured by the mother. A separate measure is used for each baby, and the measure is washed and hung to dry. The washbasin is scrubbed and boiled after each use.

Under nursing supervision the mother dresses the baby's cord when necessary. She also attends to other minor treatments that may be required, e. g., eye drops, painting of pustules, and rashes. A separate tray is supplied for each baby requiring treatment of infection. All solutions used are dispensed in one-ounce bottles. Each bottle of solution is used only for one baby. The mothers are accommodated in four-bed cubicles. Individual equipment is supplied for each baby. Mothers are supplied with sterile nipple trays daily.

Equipment for Baby.—Equipment includes cot, mattress cover (plastic), baby linen (kept in basket which clips on the end of the cot), soap (supplied by the mother), soap dish, buttock tray (swabs and tap water in kidney trays and bowls, covered with sterile towel), and other trays which may be required (eye or cord).

The mothers are encouraged to have short fingernails and are instructed in the principles of hand washing. Mothers are instructed to wash their hands before feeding their baby, before changing napkins, before any surgical procedure, after the use of handkerchiefs, after personal toilet, and so forth. Paper towels are provided, and basins have elbow controlled taps; bins are supplied for the soiled paper towels (foot pedal type). Mothers are encouraged to use disposable handkerchiefs. Disposable napkins are provided and are used inside the toweling napkin. The baby may be changed in its cot or on its mother's bed. The danger of placing her baby on another mother's bed is explained, and each mother is instructed not to handle any baby other than her own or any equipment belonging to another baby or mother.

Each baby is inspected daily for signs of infection by the nursery sister. The baby is handled only by the mother during this inspection. The windows in the nursery are kept open at the top to insure adequate ventilation of the unit. Babies are returned to the nursery during visiting hours, at night, and during ward cleaning procedures.

It is hardly necessary to emphasize that the staff must be enthusiastic about the scheme; one unconvinced member can do much damage. Enthusiasm for the scheme should be fostered by lectures to the staff. These include such topics as the psychological aspect of the scheme, immunity and resistance.

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PROBABILITY LEVELS

To the Editor:—In his reply to my criticism in The Journal, April 30, page 2111, Dr. Horn does not meet the issue. He says he "cannot agree with Dr. Zeisler's comment that a probability level of 0.01 is necessary for 'statistical significance.'" I had made no such comment. I said that the term as generally used in the medical literature meant that p is not more than 1/100, which is true. Dr. Horn, is, of course, entitled to use it differently, but not without comment, whereas in the summary of the article it was stated only that "These differences are statistically significant"; it was not pointed out that the term was used differently than is the present custom. Dr. Horn makes no reference to my chief criticism, namely, that two of the three cells of patients "are too small to be used in any serious statistical calculation."

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Chicago 11.

PULSELESS DISEASE

To the Editor:—In The Journal, April 23, page 1985, appeared an abstract of a case report of a patient with pulseless disease. In the abstract there is a statement, just as there was in the original paper in the *British Medical Journal*, Dec. 26, 1959, page 1439, to the effect that the case under discussion is "the first one from India." This claim for priority was subsequently disputed. Letters telling of similar cases, previously reported from India, were published in the correspondence section of the *British Medical Journal* (Feb. 13, p. 502, and March 12, p. 804).

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MEDICAL FILM REVIEWS

A New World for Peter: 16 mm., color, sound, showing time 22 minutes. Prepared in 1959 by the Parents' Committee of the Children's Ward, Tompkins County Hospital, Ithaca, N. Y., in cooperation with the Tompkins County Medical Association and the staff of the hospital. Procurable on rental ($7.50) or purchase ($175) from Parent's Committee of the Children's Ward, Inc., Box 23, Ithaca, N. Y.

The primary purpose of this film is to prepare children for hospitalization and to inform the public about the services which hospitals must provide, from laundry to laboratory, in pediatric care. Its presentation is unusual; the child-patient, Peter, carries on most of the dialogue and describes what is going to happen to him during his hospitalization as told to him by doctors and other hospital personnel. He is allowed to see other patients in the hospital who have various medical problems, and he is prepared for the laboratory and the medical and surgical procedures to which he will be subjected. There is also a description of such ancillary hospital services as the book cart, laundry, blood bank, pharmacy, dietary department, and hospital gift shop. In this particular hospital a well-organized playroom is available for the pediatric patients. This ideal situation, however, does not exist in all hospitals. The photographic quality of this film is generally acceptable, and Peter's narration lends realism to the film's message for the viewer. This film is highly recommended for such lay groups as parent-teacher associations.

New Films Added to A. M. A. Motion Picture Library

Surgical Anatomy of the Pulmonary Hilum: Part I: The Right Lung: 16 mm., color, sound, showing time 22 minutes. Prepared by Edward A. Boyden, Ph.D., and Franklin R. Smith M.D. Seattle. Produced in 1959 in the Department of Medical Illustration, University of Washington, School of Medicine, Seattle, under a grant from Pfizer Laboratories. Procurable on loan from American Medical Association, Motion Picture Library, 535 N. Dearborn St., Chicago 10, and Pfizer Laboratories, Division of Chas. Pfizer Inc., 630 Flushing Ave., Brooklyn 6.

The purpose of this film is to teach the practicalities of the anatomy of the pulmonary hilum. Shown are the anatomical structures which the surgeon must expose and recognize in dealing with pulmonary lesions of the right lung. Scenes from six operations are presented, dealing primarily with topographical relations of the anterior, posterior, and interlobar aspects of the hilum, and are prefaced by colored drawings based upon frames of the film. Although surgical techniques, as such, are not emphasized, the method of stripping diseased segments from the lung without injuring the healthy adjacent tissue is demonstrated. The anatomy is well displayed and further reinforced by colored drawings. From a technical point of view, the film is outstanding. It is recommended as an aid to the teaching of anatomy of the lung to students, interns, and residents. This film also serves as an excellent review for thoracic surgeons.

Beyond the Shadows: 16 mm., color, sound, showing time 26 minutes. Cleared for television. Produced in 1959 by Western Cine Productions, Denver, for the Colorado State Department of Public Health. Procurable on loan (service charge $3) from American Medical Association, Motion Picture Library, 535 N. Dearborn St., Chicago 10.

This film reveals some of the problems and causes of mental retardation. Its primary intention is to stimulate general community groups to initiate programs of aid for mentally retarded children in their own areas with the help of local public and private agencies. All phases of mental retardation are discussed, including problems during infancy, early childhood, the school years, young adulthood, and older adulthood. The film indicates how members of the community in conjunction with public health nurses can combine forces to develop further resources and help integrate the retarded child into the community. Statistics are given as to the amount of mental retardation in this country, and the statement is made that the retarded child also lives, in many cases, in a retarded community which has few facilities for community help. The photography of this film exemplifies an outstanding combination of artistry and an informational medium used to present a message of importance. This excellent film is highly recommended for pediatricians, general practitioners, house officers, medical students, and the lay public.

Intermittent Positive Pressure Breathing IPPB/I: Its Clinical Applications and Administration: 16 mm., color, sound, showing time 31 minutes. Prepared in 1960 by Theodore H. Noehren, M.D., Buffalo. Procurable on loan (service charge $2) from American Medical Association, Motion Picture Library, 535 N. Dearborn St., Chicago 10.

This instructive film sets forth the uses of intermittent positive breathing of the inspiratory type. Postoperative management as well as medical lung conditions are shown. Although one particular machine is used here, the author states there are others which may be used for the same purposes. Viewers might disagree somewhat as to the need for use of this type of treatment in all of the cases suggested. However the decision on this point would rest with problems presented by the individual patient. The film mentions the therapist and suggests that, in using the machine, he report any untoward reactions to the physician. The entire technique appears simple enough that a therapist need not be specially trained in order to achieve more universal application of IPPB/I technique in a hospital. A nursing staff should be able to apply this treatment, but, more important, the patient should learn to use the equipment properly. The theme of the film is that, with assiduous long-term help of the right kind, life can be made bearable for these respiratory cripples. The photographic quality of this motion picture is good and the pace of the narration is maintained at a comprehensible rate. It is recommended for internists and surgeons.

ABSTRACTS FROM THE LITERATURE

INTERNAL MEDICINE

Corticotropin and Corticosteroid Therapy in Chronic Polyarthritis: Seven and One-Half Years' Study. J. H. Solem and O. Rømcke. Nord. med. 63:11-15 (Jan. 7) 1960 (In Norwegian) [Stockholm].

Patients with rheumatoid arthritis were treated with cortisone, corticotropin, and prednisone during 2 periods of 3 years and 9 months ending in 1958. In the 1st period 68 patients were given hormone treatment for from 3 to 43 months; in the 2nd period 28 patients received continuous treatment for from 6 to 45 months. In 6 cases treatment was discontinued because of complicating diseases, none fatal, possibly due to the hormone treatment. Of the patients in the 1st group, 12 are still under steroid treatment after 4½ to 8 years; neither hypertension nor glycosuria has developed. Marked osteoporosis was registered in 4 patients after 3 or 4 years of treatment; prednisone was withdrawn from 3 patients, and the 4th is receiving treatment with anabolic steroids. No manifestations of adrenal insufficiency due to the hormone treatment have been noted. The number of patients able to work increased from 4 to 27 in the 1st group and from 6 to 22 in the 2nd group. The authors conclude that some patients with chronic polyarthritis who fail to benefit from rest in bed and salicylate, phenylbutazone (Butazolidin), and gold treatment can improve on treatment with corticosteroids. A relatively small group of patients seems to be fitted for this treatment, which usually is not considered until the disease has progressed in spite of other therapy, or because phenylbutazone or gold treatment causes complications.

Hypocalciuria as a Sign of Glomerular Insufficiency. A. Lichtwitz, S. de Seze, R. Parlier, D. Hioco, and Ph. Bordier. Presse méd. 68:167-169 (Jan. 30) 1960 (In French) [Paris].

Fifty-five patients, over 60 years of age, who were suffering from different disorders, underwent a complete physical examination, including determinations of glycemia, azotemia, albuminuria, and calciuria. Albuminuria was found in 2 patients with no sign of renal insufficiency; azotemia was found in 2 more patients, and in 1 of them it was associated with mild symptoms of glomerular insufficiency. The calcium level in calciuria was below 70 mg. per 24 hours in 17 patients; in 12 of these the glomerular clearance was definitely reduced. The authors conclude that a hypocalciuria below 50 mg. per 24 hours is the rule in hyperazotemic patients, and that a normal or an elevated calcium level associated with hyperazotemia suggests the presence of a tubular lesion or of an osteopathy due to hyperosteolysis in patients with myeloma or a secondary bone cancer. It is pointed out that, while 55 blood urea determinations gave only 1 diagnostic clue, the urinary calcium level led to the diagnosis of renal insufficiency in 1 out of every 4 patients examined.

The constant finding of decreased calciuria in azotemic nephritis led the authors to a systematic study of the urinary calcium level in a series of nephropathies without hyperazotemia. They found that a definite hypocalciuria was present in all the patients in whom the clearance indicated reduction of glomerular filtration. Thus, investigation of hypocalciuria is probably the best method of diagnosing renal insufficiency, and it should replace determination of the blood urea level as a routine test in biochemical investigations.

Activity of Hepatic Arginase in Patients with Hepatic Coma. G. Ugarte, M. E. Pino, and J. V. Escobar. Rev. méd. Chile 87:970-974 (Dec.) 1959 (In Spanish) [Santiago].

The activity of hepatic arginase was determined in liver specimens obtained from 2 groups of patients: (1) an experimental group composed of 12 patients who died in hepatic coma (10 had liver cirrhosis and 2 had fulminant hepatitis) and 2 patients who died of liver cirrhosis without signs of hepatic coma and (2) a control group composed of 6 patients who underwent laparotomy for a condition without hepatic involvement and 4 patients who died of different diseases, also without liver involvement. On the experimental group, besides clinical examination, several laboratory tests had been performed. Arterial ammonia values had been determined in 5 patients, and the blood arginase activity had been measured in 9. The arterial ammonia level was elevated, varying between 1.68 and 2.6 mcg. per cubic centimeters of blood, while the normal value is below 1 mcg.

The average arginase activity in the control group was 9.5 + 3.72 μM of urea per milligram of protein, while the average value in the group with hepatic disease was 2.5 + 1. 16 μM per milligram. The difference between the 2 averages is statistically significant. The decrease in arginase activity may be caused by 2 mechanisms: 1. It may result from

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The place of publication of the periodical appears in brackets preceding each abstract.

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a failure of the liver in synthesizing proteins. 2. It may be related to the liberation of the enzyme into the blood stream by the damaged cell. The authors see a relationship between these mechanisms and the presence of hyperammoniemia in patients with hepatic coma, and they suggest that the low hepatic arginase activity may be responsible for the failure of treatment with arginine in many cases, in contrast to the results obtained in the experimental studies. A second hypothesis is that the decrease in hepatic arginase activity may be another mechanism leading to the hyperammoniemia which is so frequent in patients with hepatic coma.

SURGERY

Elective Splenectomy: An Analysis of 220 Operations. C. E. Sedgwick and A. H. Hume. Ann. Surg. 151:163-168 (Feb.) 1960 [Philadelphia].

The authors present an analysis of 220 splenectomies performed at the Lahey Clinic, Boston, from 1939 to 1957. The mortality in the entire series was 7%, and the morbidity 34%. Liver disease was the indication for splenectomy in 83 patients. Of these, 26 underwent splenectomy between 1939 and 1948; of the 57 who were treated between 1949 and 1957, splenectomy and a shunt operation were carried out in 29, and splenectomy without a shunt in 28. The other indications for splenectomy were: idiopathic thrombocytopenic purpura in 40 patients; congenital hemolytic anemia in 30; acquired hemolytic anemia in 22; splenomegaly with hypersplenism (neoplastic) in 16; splenomegaly with hypersplenism (non-neoplastic) in 15; cysts in 9; and primary splenic neutropenia and pancytopenia in 5. Each of these groups of patients is discussed.

The decision to employ splenectomy is not to be regarded lightly. The operation may be technically difficult, and the postoperative path strewn with obstacles. Careful selection of cases is essential, and complete medical and hematological study will help in this selection. A mistaken diagnosis may cause the patient to undergo a serious operation without benefit, or an error in judgment may cost his life. The hazards associated with splenectomy are tabulated.

Patients who have bleeding esophageal varices, with or without hypersplenism, constitute a special problem. The authors are convinced that portal decompression by splenorenal or portacaval shunt is indicated in the majority of these cases. The choice of operation is as yet unsettled. The wider use of splenoportography makes them wonder whether a two-stage operative approach (splenectomy with subsequent portacaval shunt) might not be safer for selected patients with severe hypersplenism but no active variceal bleeding, especially if the spleen is not palpable and the liver function moderately deranged (indicating active liver disease) despite prolonged treatment. The degree of splenomegaly is a useful guide to the size of the splenic vein, and this is an important preoperative consideration.

The conditions which respond most favorably to splenectomy are, fortunately, associated with the lowest morbidity and mortality. When the diagnosis of chronic idiopathic thrombocytopenic purpura or congenital hemolytic anemia has been firmly established, the surgeon should feel no hesitancy about performing splenectomy.

Late Results of 300 Cholecystectomies Performed under Peroperative Radiomanometric Control. C. Debray, M. Roux, R. Le Canuet, and J. Thomas. Semaine hôp. Paris 36:296-308 (Jan. 28) 1960 (In French) [Paris].

The authors report on a 3-year follow-up study of 300 patients who underwent cholecystectomy under radiomanometric control. The interval between the operation and the survey varied from 2 years (85 patients, 28% of the series) to 10 years (10 patients, 3.3% of the series). Two hundred twenty-four patients (75%) were examined directly 2 or 3 times during the study. The remaining 76 patients were contacted by questionnaire. Many patients underwent supplementary examinations to determine the nature of the lesions associated with the original cholecystic disease. One hundred one patients were studied by venous cholangiography for investigation of the postoperative course in the main biliary tract.

The over-all results of the 300 cholecystectomies were classified as excellent, incomplete, and failures. Excellent results meant complete and definitive elimination of the disorder motivating the operation, even when mild disturbances were experienced by the patients, such as diarrhea or constipation, temporary headaches, or minimal digestive troubles. Incomplete results meant recurrence in a milder form of some symptoms related to the lesion which had motivated the operation. Patients who obtained incomplete results still felt mildly painful reactions in the hypochondrium on the right and had persistent manifestations of dysfunction. Failure meant that the major disturbances leading to the operation remained unchanged. Two hundred fifty-nine patients (86.3%) had excellent results; 25 patients (8.3%), incomplete results; and 16 (5.3%), no results. A breakdown, by the nature of the lesion ascertained at the operation, showed that excellent results were obtained in 30 (75%) of 40 cholecystectomies for nonlithiasic gallbladder, in 159 (90.3%) of 176 operations for lithiasic gallbladders, and in 70 (83.3%) of 84 cholecystectomies for a gallbladder condition associated with other diseases. Data from 101 cholangiographies showed that the caliber of the main biliary tract was unchanged in 62 patients, decreased in 5, and increased in 34. The authors stress the need for a thorough evaluation of the indications for operating, and the importance of a complete extrabiliary examination before any surgical treatment. They think that at the time of operation the information given by the radiomanometric study is irreplaceable.

DERMATOLOGY

Hypnosis and Dermabrasion. J. W. Burks. A. M. A. Arch. Dermat. 81:378-380 (March) 1960 [Chicago].

The success of hypnosis in facilitating the whole procedure in the planing of a nevus flammeus near the orbit of a 9-year-old girl led to incorporation of this method into the author's planing routine. Results, based upon the combined reports of patients, their families, and their associates, indicate that there is some degree of success in the application of hypnosis in every patient. The state of hypnosis achieved is generally one of a mild-to-medium hypnotic stage. There is a visible elimination of signs of apprehension, such as tenseness of muscles, rigidity or movement of hands and feet, turning of the head from side to side, as well as elimination of postoperative shock reactions (nausea, vomiting, and syncope). Posthypnotic suggestive phenomena successfully eliminated postoperative discomfort for 3 days in one patient.

The hypnotizability of patients depends upon their willingness to cooperate, their ability to imagine, their need of motivation, and the prestige of the hypnotist. The patient may be indoctrinated with the phenomena of hypnosis during weekly visits to the dermatologist, so that the time of treatment need not be prolonged. A deep anesthetic stage of hypnosis would be the ideal stage, were it not for the time-consuming factor.

PEDIATRICS

Hypophosphatasia. J. C. Rathbun. Helvet. paediat. acta 14:548-553 (Dec.) 1959 (In English) [Basel, Switzerland].

In 1947 the author was able to study an unusual case of incomplete calcification of bone, resembling rickets but associated with decreased tissue and serum alkaline phosphatase. Because of the low-tissue phosphatase, this was called hypophosphatasia. Subsequently other authors reported similar cases, a total of 44. An incidence of 1 in 100,000 births has been calculated. According to the age of onset, 3 groups have been differentiated.

In patients of group 1, symptoms appear before the child is 6 months old. These infants fail to thrive, are constipated, and vomit; convulsions and attacks of cyanosis may occur. These children have severe rickets and hypotonia. Bony tenderness and irritability are common. There may be pathological fractures, and craniostenosis and kyphosis may develop. The bones show defective calcification as in rickets. Characteristically, the skull has a well-calcified base with an almost uncalcified vault in severe cases. In group 2 patients, in whom signs become manifest after 6 months of age, they are less severe. Premature loss of teeth may occur; genu valgum and other orthopedic deformities may be seen. The metaphysial trabeculae may be coarse and distorted. The skull is usually normal or shows increased lacunar markings. In group 3 patients, the disease is recognized in adult life; fragile long bones with fractures and mild osteoporosis are the rule. Many patients show stunted growth.

Serum alkaline phosphatase may range from nearly zero to 40% of the lower limit of normal. Serum calcium level is elevated in the severe cases, while serum phosphorus is normal. Phosphorylethanolamine has been demonstrated in the urine. This substance is rarely found in normal urine. It is interesting that phosphorylethanolamine appears in the urine of patients with celiac disease, hypothyroidism, and scurvy. Alkaline phosphatase will hydrolyze this substance in vitro. The histological picture in bone is that of severe rickets. The kidneys usually show a disturbance in the region of the renal tubules with calcification. The disorder is hereditary. Treatment is difficult to assess in view of the cyclical course. Vitamin D appears to be dangerous in the face of hypercalcemia. Cortisone has been observed to produce mineralization of bone in a few cases.

UROLOGY

Renal Agenesis and Dysgenesis. D. J. B. Ashley and F. K. Mostofi. J. Urol. 83:211-230 (March) 1960 [Baltimore].

These studies are concerned with renal agenesis and severe dysgenesis, both unilateral and bilateral, and with an investigation of associated defects of the urogenital tract and other organs in 364 cases from the files of the Armed Forces Institute of Pathology, Washington, D. C. The cases were taken from a collection of 245,000 autopsy protocols and related slides. The incidence of anomalies of the kidney is, therefore, of the order of 1 in 650. Eleven cases were seen in which there was development of the kidney without a ureter being present. It is suggested that the formation of the definitive kidney depends both on the presence of the ureteric bud and on the existence of an adequate metanephrogenic blastema, and that the ureteric bud develops in response to induction from the developing metanephros.

The authors feel that a new hypothesis of the embryogenesis of the renal tract becomes necessary. They suggest that the potentiality for renal differentiation rests in the structures of the nephrogenic ridge. Both the pronephros and the mesonephros form their tubules and duct in response to organizers as yet unknown, and the stimulus for the outgrowth of the ureteric bud from the lower end of the mesonephric duct arises in the metanephric blastema at the lower end of the nephrogenic ridge. Full development of the kidney depends on the whole of this mechanism being intact.

On the basis of this hypothesis, the authors propose a new 6-group system of classification of renal agenesis and dysgenesis, and differentiate 2 main groups: 1. There is complete failure of differentiation of the nephrogenic ridge. 2. There is failure of development of the nephrogenic ridge after the formation of the pronephric and mesonephric ducts. Under the latter there are 4 subgroups: 1. There is failure of the metanephros with failure of induction of the ureteric bud. 2. Induction of the ureteric bud is present, but the potentiality of the metanephros for forming renal tissue is deficient, either completely or partially. 3. Induction of the ureteric bud is absent, but the metanephros retains the ability to form renal tissue. 4. There is failure of the nephrogenic ridge on one side, but the ureteric bud of that side is induced by the contralateral metanephros and is attracted to the opposite side of the body. The etiology of renal agenesis and dysgenesis is discussed. In many instances there are anomalies of other parts of the body, and it is suggested that all the concurrent defects are due to extraembryonic factors, which act on any part of the embryo undergoing critical stages in development at the time of action of the external stimulus.

Bacteriuria and Urinary-Tract Infections in Hospitalized Patients. A. L. Kaitz and E. J. Williams. New England J. Med. 262:425-430 (March 3) 1960 [Boston].

The authors report on 309 unselected patients who were admitted to the medical and surgical ward services of the Beth Israel Hospital in Boston between September and November, 1958, and from whom clean-voided urine specimens were obtained. Significant bacteriuria, defined as more than 100,000 pathogenic bacteria per cubic centimeter of urine, was present in the specimens of 53 (17.2%) of the 309 patients. Only 2 of the 309 patients entered the hospital with a clinical picture of acute pyelonephritis. For most of the patients with bacteriuria, symptoms referable to the urinary tract were absent. The condition was usually overlooked clinically because of failure to search for bacteria in stained specimens of urine and by urine culture in the absence of pyuria.

The significance of bacteriuria was assessed in terms of its relation to clinically apparent urinary-tract infections. It was evident that such infections occurred in relation to genitourinary-tract instrumentation. Patients without bacteriuria on admission did not acquire clinical urinary-tract infection unless bacteriuria developed in association with genitourinary-tract instrumentation. Clinical urinary-tract infections were the most common indication for chemotherapy in this population group. Properly controlled suppression of bacteriuria with urinary antiseptics and improved hygiene may help to reduce the incidence of urinary-tract infections acquired in the hospital in association with urinary-tract instrumentation. Asymptomatic bacteriuria, symptomatic urinary-tract infections, and impaired renal function appear to be related. More frequent detection and study of patients with bacteriuria will lead to more effective treatment and to a better understanding of the clinical importance of this finding.

OPHTHALMOLOGY

Tobacco Amblyopia. H. S. Hedges. Virginia M. Month. 87:144-145 (March) 1960 [Richmond].

The author reports 4 cases of eye damage from tobacco. Sudden blackouts may occur, probably caused by constricting spasms of some of the cerebral vessels. The 1st patient was a trailer truck driver. He said that sometimes, when driving, suddenly everything went black before him; he could not see a thing and had to get off the road as best he could and wait till his sight came back. The author ordered him to stop smoking, and the man reported later that he had not had a blackout since he had stopped. Not all these blackouts are binocular; when only one eye is involved, often the upper extremity of the same side is paralyzed.

Premature presbyopia occurs, especially among woman smokers, who generally first complain of dull headache and asthenopia on close work. The 2nd case presented was that of a 38-year-old man who was unable to read newspaper print even with a glass intended for one 10 years older. When he stopped chain-smoking, all trouble disappeared. If these cases are not arrested, a central scotoma develops for red and green, which is relative at first, but which gradually increases till all perception of central red and green is gone.

A 50-year-old man had lost his job because of defective eyesight. Since his eyes indicated damage from tobacco, he was asked to stop smoking, and he has recovered. The 4th patient was a 62-year-old man, a heavy smoker, who had been told by ophthalmologists that nothing could be done for his advancing blindness. When he was ordered not to smoke for 3 months, his uncorrected vision recovered to 20/30. Advanced cases of eye damage from tobacco occur in long-time smokers, and the cigar is the worst offender, though the cigarette is by no means harmless. Moderate smoking of mild tobacco does not seem to do much harm.

Routine Tonometry in 5,000 Patients for Detection of Early Glaucoma. J. E. L. Bendor-Samuel, W. May and H. Reed. Brit. M. J. 1:853-855 (March 19) 1960 [London].

It has been routine practice in the eye department of the Winnipeg Clinic during the last 4 years to measure the intraocular pressure of every patient above the age of 40 years, nurses having been trained to perform this simple test. Among

5,000 patients 43 (0.9%) were found to have clinical signs of glaucoma, but 217 (4.3%) were found to have a pressure above 25 mm. Hg in one or both eyes, but no other clinical sign of glaucoma. These 217 patients were advised to undergo further investigation; 82 failed to report for further tests, but of the 135 patients who underwent further studies, 92 were found to be free from glaucoma, and 43 were found to have the disease. Thus, a total of 86 (1.7%) of 5,000 patients had glaucoma. The first step in the study of those who, on routine testing, had a pressure above 25 mm. Hg was to repeat the test. Then gonioscopy was done to determine whether the corneoscleral angle is of the wide or the narrow type. If the angle is narrow, a mydriatic test is performed, unless the pressure is very high. If the angle is wide, or the mydriatic test is negative, a water drinking test is done. The authors believe that routine tonometry should be performed as part of the eye examination of every patient over the age of 40.

Giant-Cell Arteritis: A Review of 35 Cases. R. W. Ross Russell. Quart. J. Med. 28:471-489 (Oct.) 1959 [London].

The author reviews the clinical features of 35 cases of giant-cell (temporal) arteritis. The course of the disease is divided into 3 stages: the stage of headache; the stage of visual complications; and the stage of systemic complications. Visual disturbance in giant-cell arteritis may result from an ophthalmoplegia or from vascular lesions in the optic nerve and retina. It is important to distinguish the 2 causes, as the prognosis is different in the 2. Ophthalmoplegia occurred in 5 patients. Diplopia usually appeared shortly after the onset of headache. The lesion involved the 3rd and the 6th cranial nerve; while its onset was sudden, recovery required from 2 to 8 weeks, a sequence which suggests vascular occlusion. Visual failure occurred in 16 patients, 5 of whom became completely blind, 5 were blind in one eye, 5 had considerable visual impairment, and 1 recovered.

It is fortunate that ophthalmic arteritis is almost always preceded by temporal arteritis, because this may permit preventive treatment. Scalp tenderness, difficulty in opening the mouth, and pain on eating were frequent symptoms, but many patients are not seen until after the onset of visual failure. Steroids given before the onset of visual symptoms prevent the spread of the disease to the eyes, but they have little effect on the progression of an ocular lesion once it has occurred. It is suggested, therefore, that all patients with giant-cell arteritis should receive steroids as soon as the diagnosis is made, and for some months afterwards.

Sytemic complications that may follow or accompany cranial arteritis include general arteritis with skin or visceral lesions, and varieties of peripheral neuritis, or a generalized skeletal disorder with muscle pain and wasting. Steroid therapy is particularly effective in patients with muscular symptoms, but is considerably less effective in dealing with other complications.

THERAPEUTICS

Clinical Investigation on the Use of Heart Extract. A. A. Villela, L. Abitbol, and G. Leszeck. Rev. brasil. med. 17:1-8 (Jan.) 1960 (In Portuguese) [Rio de Janeiro].

Forty-seven patients with coronary insufficiency were treated with heart extract for periods of from 3 to 10 weeks. The average dosage was an intramuscular injection daily or every other day, plus a tablet taken 3 times daily. Anginal pain disappeared completely in 7 patients (14.9%), and was greatly relieved in 31 (65.9%), together with improvement in other subjective symptoms. Six patients (12.8%) experienced only a moderate improvement, and 3 (6.4%) experienced no improvement.

Electrocardiographic changes were classified as excellent in 8 patients (complete normalization of previously altered leads and repolarization); good in 20 patients (42.5%) who had had primary alterations in the T wave, and in whom the leads became more positive and closer to normal; fair in 5 patients (10.6%) in whom the effects of the treatment were not clear; and negative in 14 patients (29.9%). These results indicate that this treatment is effective in arteriosclerotic cardiopathies.

Iproniazid in Treatment of Angina of Effort. R. Fife, G. Howitt, and J. Stevenson. Brit. M. J. 1:692-694 (March 5) 1960 [London].

The authors present a controlled clinical trial of iproniazid in 51 patients with angina pectoris. The trial had begun soon after the favorable report of this drug in angina pectoris had appeared, and before the extent of the toxicity of the drug had become apparent. The early promise of the drug and the suggestion of a fundamentally different mode of action from the commonly used vasodilators were the reasons for this clinical trial. The trial was conducted on a "double-blind" basis, with use of control tablets identical in appearance with iproniazid. The dosage was 50 mg. 3 times daily after meals, and drug and placebo were each given for a 3-week period in varying sequence.

The use of a drug with a very high incidence of side-effects tends to destroy the double-blind design of the therapeutic trial, as the clinicians can hardly fail to recognize which is the active drug. The authors feel that in such circumstances conclusions must be particularly cautious, and cannot claim the total lack of possible bias as fully double-blind trials. With this in mind, they limit their conclusions to stating that they have been unable to confirm any striking value of iproniazid in angina pectoris, that, except in severe cases, it was of no greater efficacy than the placebo, and that even in the severer cases any possible benefit was at best marginal, numbers of such cases being too small to be statistically conclusive. Side-effects were frequent and troublesome.

The Use of Nitrogen Mustards in the Treatment of Malignant Lymphatic Diseases. J. Rabenko and L. M. C. Urquiza. Prensa méd. argent. 46:2449-2454 (Oct. 9) 1959 [Buenos Aires].

Fifty-one patients (37 males and 14 females) with malignant lymphatic diseases were treated with chlormethine, either alone or associated with other therapeutic agents. There were 33 patients with malignant lymphogranuloma (Hodgkin's disease), 11 with lymphosarcoma, 6 with reticulosarcoma, and 1 with giant follicular lymphoma (Brill-Symmers disease). The patients' ages ranged from 10 to 80 years, with the highest frequencies in the 40-to-60-year age bracket. Chlormethine was injected intravenously in a daily dose of 1 or 2 ampuls of 5 mg. dissolved in 20 cc. of isotonic dextrose solution, and 2 ampuls of vitamin B_6. A subjective improvement was noted in most patients from the beginning of the treatment. Only 6 patients (11.7% of the series) did not experience relief of symptoms. The affected lymph nodes decreased in size, especially in patients with Hodgkin's disease, although no direct relationship was found between a definite dosage and the degree of improvement. The most common hematological effect of the nitrogen mustard treatment was leukopenia, which could be neutralized by a combination of blood transfusions and corticoid therapy. The condition of the liver must be watched during the administration of chlormethine. As long as the hepatic function is preserved, the treatment is well tolerated. Hepatic insufficiency means unfavorable prognosis and makes chemotherapy difficult.

Responses to "Physiologic" Doses of Folic Acid in the Megaloblastic Anemias. R. A. Marshall and J. H. Jandl. A. M. A. Arch. Int. Med. 105:352-360 (March) 1960 [Chicago].

In order to compare the therapeutic effect of folic acid in small "physiological" amounts with that of the larger "pharmacological" doses usually administered, the authors studied 5 women, between the ages of 51 and 84 years, and 1 84-year-old man with megaloblastic anemia at the Boston City Hospital. Using currently available laboratory criteria, an attempt was made to establish whether the underlying nutritional deficiency was of cyanocobalamin or of folic acid. Each patient received a course of small (physiological) doses of folic acid, 0.4 mg. being injected intramuscularly daily; this was followed by a course of larger daily doses of folic acid, 15 mg. being injected intramuscularly. Three patients were given a 3rd therapeutic course of 30 mcg. of cyanocobalamin intramuscularly daily. Of the 6 patients, 3 with folic acid deficiency responded well to the small doses of folic acid without further response to the larger doses. The other 3 patients with cyanocobalamin deficiency and pernicious anemia had little or no response to the small doses of folic acid, but responded well to the larger doses. The subsequent parenteral administration of cyanocobalamin during a 3rd therapeutic period had no further hematological effect in any of these patients.

These findings indicate that the usual therapeutic doses of folic acid exceed those necessary for replacement therapy and are inappropriate for use in therapeutic trials. The use of more nearly physiological doses of either cyanocobalamin or folic acid permits one to identify deficiencies of these 2 vitamins without the aid of elaborate biochemical or microbiological measurements. The observations made in the 6 patients substantiate previous evidence that the normal daily requirement for folic acid in adults is less than 0.5 mg. and suggest that this, rather than a larger amount, should be used in the prophylaxis of simple dietary deficiency. Patients with megaloblastic anemia who fail to respond to physiological amounts given parenterally of either cyanocobalamin or folic acid, but who do respond to large amounts of folic acid, may be considered to have an abnormality of folic acid utilization, rather than folic acid deficiency.

Coccidioidal Granuloma After Treatment with Amphotericin B: Report of a Case. K. C. Baker and S. R. Kemberling. A. M. A. Arch. Dermat. 81:373-377 (March) 1960 [Chicago].

A 3-year-old boy was admitted to the San Xavier Indian Hospital in Tucson, Ariz., with weeping lesions on the scrotum, gluteal fold, and about the arms. A diagnosis of coccidioidal granuloma was established, and the patient received a series of 6 x-ray treatments which seemed to eradicate the lesions. Two years later the lesions recurred on the same areas. Treatment with local antibiotic ointment, hydrocortisone, and tetrahydroxyquinone was unsuccessful, and the patient's condition on the perineal region became so involved that he no longer controlled his bowel movements. A radical excision of the granulomatous plaques, followed by thickness graft and a permanent colostomy, was considered, but the results of a complement-fixation test contraindicated the operation. Treatment with amphotericin B given intravenously was started in an initial daily dose of 0.5 mg. per kilogram of body weight; this dose was increased to 0.75 mg. in the 2nd week and to 1 mg. in the 3rd week. The drug was diluted in 500 cc. of sterile water and given over a period of 4 to 6 hours. The preparation was administered daily during 6 weeks, then every other day. Aspirin (0.6 Gm.), promazine, and diphenhydramine (25 or 50 mg.) were given 1 hour before the intravenous injection, and repeated every 4 hours, if necessary. One cubic centimeter of heparin solution was added to the intravenous injection to prevent clotting in the vein. After the administration of a total dose of 800 mg., the lesions had completely disappeared, leaving only soft pigmented scars. The advisability of administering amphotericin B intravenously is stressed, because of the poor absorption when given by mouth.

Notes on the Therapeutics of Pemphigus Foliaceus. M. Fonzari. Hospital 57:275-283 (Feb.) 1960 (In Portuguese) [Rio de Janeiro].

Seven female patients treated on the Service of Pemphigus Foliaceus in São Paulo, Brazil, were selected for an experimental study of the effect of a combined corticosteroid-quinacrine therapy. The patients' ages ranged from 13 to 57 years, and the duration of the disease varied from 3 to 11 months. Dexamethasone acetate was administered in the dose of 4 mg. daily, except to a 13-year-old girl who received only 2 mg. In 2 patients, whose disease was in an early stage, the regression of the lesions was evident within 10 and 18 days respectively. In the other patients the dose of 4 mg. daily had to be maintained for 95 to 111 days before a visible regression was obtained. The patient who was receiving only 2 mg. daily did not improve until her dose was increased to 3 mg. After a regression had been definitely observed, the dosage of dexamethasone was gradually decreased to 3, 2, and 0.5 mg. daily, then replaced by quinacrine hydrochloride. The only side-effect observed during the treatment with dexamethasone was increase in weight in 2 patients. Four patients suffered a relapse, and their lesions acquired a pustular aspect which subsided on the administration of penicillin. This suggests that a combined dexamethasone-penicillin therapy might accelerate the involution of the lesions. The administration of quinacrine hydrochloride was effective in maintaining the improvement obtained with the corticosteroid therapy, with the occurrence of only a slight eruption in some lesions.

PATHOLOGY

The Central Nervous System in Acute Leukemia: A Postmortem Study of 117 Consecutive Cases with Particular Reference to Hemorrhages, Leukemic Infiltrations, and the Syndrome of Meningeal Leukemia. E. W. Moore, L. B. Thomas, R. K. Shaw, and E. J. Freireich. A. M. A. Arch. Int. Med. 105:451-468 (March) 1960 [Chicago].

Of 150 patients with acute leukemia, who were admitted to the clinical center, National Institutes of Health, in Bethesda, Md., between 1953 and 1958, 141 died, and autopsies were performed on 125 (89%). The authors examined pathologically the central nervous system of 117 of these patients, 74 of whom had lymphocytic leukemia, and 43 had granulocytic (myolocytic) leukemia. Intracranial hemorrhages (intracerebral or subarachnoid) were responsible for the death of 23 patients (20%). The incidence of intracerebral leukostasis (stasis of leukemic cells) and of nodules of leukemic cells was directly related to the height of the leukocyte count shortly before death. Most of the fatal intracerebral hemorrhages were associated with the presence of these lesions. In contrast, fatal subarachnoid hemorrhages were not associated with these findings and appeared to be related to severe thrombocytopenia. Leukemic infiltration of the dura was noted in 52 (70%) of the patients with lymphocytic leukemia and in 25 (59%) of the patients with granulocytic leukemia. It was significantly commoner among children than adults and was slightly more frequent among males than females. In contrast to the high incidence of dural involvement, leukemic infiltration of the arachnoid was found in only 35 (30%) of the 117 patients with acute leukemia. Arachnoidal infiltration was significantly more frequent in lymphocytic than in granulocytic leukemia, and was also commoner in children than in adults. It was noted most frequently among boys with lymphocytic leukemia.

Perivascular infiltration, or cuffing, was observed in only 22 (19%) of the 117 patients. The amount of this infiltration and the distribution of cases were similar to that noted for arachnoidal involvement. All the patients with perivascular cuffing also showed leukemic infiltration within the arachnoid. Diffuse leukemic infiltration within the cerebral tissues was noted in only 5 patients. In one of these this infiltration, associated with marked perivascular cuffing, was noted in the hypothalamus of operation the information given by the radio-during life. Arachnoidal infiltration, perivascular infiltration, and internal hydrocephalus were significantly commoner among patients with the syndrome of meningeal leukemia than among patients who had not exhibited this syndrome. Symmetrical dilatation of all 4 ventricles, the foramens of Monro, and the aqueduct of Sylvius was found in 15 (75%) of 20 patients with meningeal leukemia. Leukemic infiltration in the arachnoid, particularly along the brain stem, may have resulted in obstruction of cerebrospinal fluid flow, increased intracranial pressure, hydrocephalus, and the syndrome of meningeal leukemia.

Cerebrospinal fluid (C. S. F.) findings, obtained within one week of death in 21 patients, were correlated with the degree of arachnoidal infiltration noted in these patients at autopsy. The C. S. F. white cell count appeared to be the most reliable parameter by which one might estimate, during life, the degree of arachnoidal infiltration in a given patient. The reported data emphasize that involvement of the central nervous system is of major importance in acute leukemia as regards both natural history and treatment of neurological complications.

BOOK REVIEWS

Pediatric Dermatology. By Henry H. Perlman, M.D., Phar.D., Clinical Professor of Pediatrics, Jefferson Medical College, Associate Professor of Pediatrics, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Cloth. $18. Pp. 477, with 203 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1960.

This book substantiates one definition of the specialist, i. e., a man who knows more and more about less and less. The author is qualified for this task by his training in both pediatrics and dermatology, his certification by both specialty boards, as well as his teaching of both subjects. The book is written from the pediatrician's viewpoint. It is not just another dermatological textbook that includes only a few subjects of particular import to children. Rather, there is reference to such things as disease incidence, differential diagnosis, and prognosis as they apply to children, and the differences, if they exist, from what may be true for adults.

The extensive formulary is a valuable part of the volume, and even in other sections there is unusual stress on therapy. Almost every page offers one or more prescriptions and definite and detailed directions for treatment. This helpful emphasis on drugs and their use naturally stems from the author's pharmacological qualifications. This work is a welcome synthesis of specialized knowledge in several fields. Yet, it is all presented in a simple and palatable style. The dermatologist should appreciate this ready reference to dosage forms and methods applicable to children, and the pediatrician will find almost all dermatoses succinctly described. The general practitioner, too, should profit by owning this handy and useful volume, which unquestionably is one of the best of its kind in English.

THEODORE CORNBLEET, M.D.

Handbook of Aging and the Individual: Psychological and Biological Aspects. Edited by James E. Birren. Paper. $12.50. Pp. 939, with illustrations. University of Chicago Press, 5750 Ellis Ave., Chicago 37; Cambridge University Press, Bentley House, 200 Euston Rd., London, N. W. 1, England; University of Toronto Press, Toronto 5, Canada, 1959.

The Inter-University Training Institute in Social Gerontology was recently created at the University of Michigan. It has as one of its important objectives the preparation of three volumes which are intended to summarize all current knowledge about human aging. This handbook, the first in the series, is divided into four parts: Foundations of Research on Aging, Biological Aspects of Aging, Aging in Environmental Settings, and Psychological Characteristics of Aging. Thirty authors contribute 24 essays on themes appropriate to the broad subject matter of the section in which they appear. According to the preface, the handbook is intended primarily for use as a reference work by graduate students and professional and scientific specialists.

As interest deepens and expands in an area of science, there comes a need to draw together the growing literature on the subject in a readily accessible and convenient form. To a limited extent this volume serves that purpose, but it is primarily and more important a collection of scholarly essays on the subject. These elucidate the ideas of the writers rather than summarizing all that has been written. Although the book does not present quite what one was led to expect, it is, in its own right, an outstandingly important contribution to the literature on aging.

While cost was undoubtedly the prevailing consideration, it is nevertheless unfortunate that the volume had to appear with paper covers. As a reference book, it will not long survive the hard usage which a work of this kind ordinarily incurs in libraries. Incidentally, the term "handbook" seems to be a misnomer for a tome of 939 pages.

THEODORE KLUMPP, M.D.

Nutrition in Health and Disease. By Lenna F. Cooper, B.S., M.S., M.H.E., Edith M. Barber, B.S., M.S., Helen S. Mitchell, A.B., Ph.D., Dean of School of Home Economics, University of Massachusetts, Amherst, and Henderika J. Rynbergen, B.S., M.S., Associate Professor of Science, Cornell University-New York Hospital School of Nursing, New York City. Thirteenth edition. Cloth. $6. Pp. 734, with 148 illustrations. J. B. Lippincott Company, E. Washington Sq., Philadelphia 5; 4865 Western Ave., Montreal 6, Canada; Pitman Medical Publishing Company, Ltd., 39 Parker St., London, W. C. 2, England, 1958.

The 13th edition of this recognized textbook, first published in 1928, continues to maintain its reputation for presenting the most recent information on basic nutrition in a comprehensive and readable manner. The nutritional requirements of all age groups and the ways of meeting these requirements are presented in part 1, entitled "Principles of Nutrition." The discussion of how the table of recommended allowances of the National Research Council should be interpreted and used is particularly timely. A new chapter on food and public health has been added to this section, discussing the various ways food is made safe for human consumption. A brief discussion acquaints the reader with the salient points of the food and drug law, including the new food additive amendment.

Part 2 is concerned with diet in relation to specific diseases and has been thoroughly revised to include a discussion of what is known about the fat content of the diet in relation to atherosclerosis. Part 3, the section on selection and preparation of food, includes recipes for gluten-free foods, low sodium dishes, and other items useful in therapeutic diets.

The tabular material in part 4 has been brought up to date and condensed. A new table listing the sodium and potassium content of foods and seasonings has been inserted. The extensive and excellent bibliography has been enlarged so that the general references are separated from the more technical references. The general references have been further subdivided into lay and professional categories. While the book has been written primarily for the student nurse as a source of accurate, up-to-date information about principles and practices of nutrition, this book should also find a place in the library of the medical student, physician, and dietitian.

EUGENE H. STEVENSON, M.S.

Electrophoresis in Physiology. By Lena A. Lewis, Ph.D., LLD. With special chapter on immunoelectrophoresis by M. D. Poulik. Publication number 385, American Lecture Series, monograph in American Lectures in Medical Physics. Edited by Otto Glasser, Ph.D. Second edition. Cloth. $5.50. Pp. 120, with 19 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

Electrophoresis, the migration of particles under the influence of an electric field, is discussed in the light of its application to biology. A chapter on immunoelectrophoresis, the study of immunity by enumeration and identification of protein components in a mixture with electrophoresis was written by M. D. Poulik, of the Child Research Center of Michigan, Detroit. Particular emphasis is placed on the value of electrophoresis in physiology and medicine. In the discussion of medicine, for example, attention is called to the use of electrophoresis on protein pathological conditions in plasma and in other bodily fluids and to the important finding that the hemoglobin level of patients with sickle cell anemia has an electrophoretic mobility different from that of normal adult hemoglobin levels. One chapter is devoted to the research and studies of the author and associates. Electrophoresis is a specialized field, and the author has brought the subject up to date by including an extensive bibliography.

HOWARD CARTER

Forensic Medicine: Observation and Interpretation. By A. Keith Mant, M.D. Cloth. $8.50. Pp. 262, with 118 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11; Lloyd-Luke (medical books) Ltd., 49 Newman St., London, W. 1, England, 1960.

Although this book was written by a British physician about his observations and experiences in connection with medicolegal investigations throughout the British Isles, it is worthy of being in the library of every physician in the United States who is occasionally called on to perform a medicolegal investigation. The principles of forensic medicine are the same in all countries. Deaths such as those due to drowning, hanging, burning, blunt impact, and poisoning leave the same distinguishing characteristics on and about the body here as they do in England.

The value of this book is its combination of brevity, clarity, and detail. It is the closest thing to a "do it yourself postmortem examination kit" that has appeared in recent years. Just about every possible type of sudden and violent death and sexual offense is specifically discussed. The investigator is told how the body will be likely to appear, what should be noted about the body and the surroundings, and what types of evidence tend to indicate the difference between a death from natural, accidental, and criminal causes. Case histories and photographs are liberally and precisely used. This is an excellent handbook for quick reference by the infrequently called coroner's physician in rural and urban communities not having a medical examiner or well-organized and full time coroner's office.

GEORGE HALL

An Atlas of Neurosurgical Techniques. By James L. Poppen, M.D., Neurosurgeon, Lahey Clinic, Boston. Cloth. $28. Pp. 522, with 248 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1960.

The author has succeeded brilliantly in illustrating, chiefly through the medium of drawings, every step in his method of performing every known neurosurgical operation on the central nervous system. The explanatory remarks are brief and to the point, and the drawings almost speak for themselves. The work of the various artists is of high quality. Some of the technical methods used by the author may shock some Halstead-Cushing disciples. His almost universal use of the rubber catheter for drainage of brain tumors is certainly not the generally accepted practice. The methods he uses to prevent extradural hematomas seem to be more time consuming than would be required for complete hemostasis before the bone flap is replaced. The author has adapted many technical principles of general surgery to neurosurgery, obviously to cut down the length of the operative procedure. To some this may seem unwise, but those who have known him and his work over many years realize that in his hands these methods have worked very well. He is known among his colleagues as a master of neurosurgical technique, and I think the careful study of his book will readily demonstrate why this is true. This book should be in every neurosurgical library. Nothing else quite like it is presently available.

R. GLEN SPURLING, M.D.

QUESTIONS AND ANSWERS

VASECTOMY

To the Editor:—*What are the medical indications for performance of vasectomy?*

A. Eugene Pflug, M.D., McCall, Idaho.

Answer.—The medical indications for performance of vasectomy to produce sterility may be eugenic, genetic, or therapeutic. With respect to the first category, 29 states have legislation that provides for the sterilization of persons who are socially inadequate. The published information of legislative actions is a study in itself (Hughes, J. E.: Eugenic Sterilization in the United States: Comparative Summary of Statutes and Review of Court Decisions, *Pub. Health Rep.*, supp. 162, Federal Security Agency, United States Public Health Service, Division of Sanitary Reports and Statistics, 1940), and even a brief summary is impossible. The phraseology of the laws varies but, generally, sterilization for eugenic reasons may be performed on persons who are feebleminded, insane, epileptic, habitually criminal, or morally degenerate. The laws are applicable to those persons who are confined in specified institutions. The safeguards of proper legal consent and due process of law must be adhered to in conformity with local laws and jurisdiction.

A complete list of reasons for performance of vasectomy on patients with genetic difficulties is impractical, since each case must be evaluated individually. Examples of such genetic afflictions are Huntington's chorea, achondroplasia, hemophilia, hereditary spinal sclerosis, progressive subcortical encephalopathy, lipochondrodystrophy, phenylpyruvicaciduria, amaurotic familial idiocy, Laurence-Moon-Biedl syndrome, Niemann-Pick disease, and cerebral symmetrical diplegia.

Similarly, it is impractical to enumerate each medical disease for which therapeutic sterilization is desirable. In general, sterilization may be performed on patients having conditions which will be aggravated by repeated pregnancies, such as chronic hypertensive vascular disease, advanced cardiac disease, and iso-immunization due to Rh blood factor.

Furthermore, in instances in which sterilization is indicated in a marital situation it makes no difference, from a legal point of view, whether it is the wife or husband who is sterilized. In other words, a vasectomy may be performed on the husband when a medical contraindication to pregnancy exists in his wife (*Christensen* v. *Thornby,* 192 Minn. 123, 255 N.W. 620 [1934]).

Before sterilization for the reasons enumerated is performed, the written consent of the patient and spouse, if there is one, should be obtained. If the patient is a minor or an incompetent, the written consent of the parent, guardian, or other person responsible for the patient's care and support should also be obtained.

Answer.—The answer is given with the assumption that the inquirer wishes to know whether or not, in the absence of any medical indication, he may ethically perform a vasectomy solely for the purpose of preventing pregnancy. The "Principles of Medical Ethics" of the American Medical Association is silent on this subject. While the "Principles" is a guide for the maintenance of a high level of ethical conduct, they do not establish the rightness or wrongness of social behavior or of human conduct generally. Whether the performance of vasectomy for the purpose of preventing conception is right or wrong is a moral and social problem which lies outside the jurisdiction of the Associations.

BALANITIS SCLEROTICA OBLITERANS

To the Editor:—*What is the etiology and the treatment of the pathological entity known as "balanitis sclerotica obliterans," also known as "balanitis xerotica obliterans" and "Stuhmer's disease?"*

LaSalle Mondor, M.D., Grand'Mere, Quebec.

Answer.—Balanitis sclerotica obliterans is a progressive, sclerosing, atrophic process involving the glans penis and prepuce with a parchment-like induration and a dry, telangiectatic surface. This process often involves the urethral meatus, causing stricture, and may involve the prepuce, causing phimosis. A disease process similar to this was first described by Fournier in France in 1866, and he called it "interstitial, or deep, balanitis." Delbanco, in 1908, described kraurosis of the penis and prepuce, which apparently was similar to this condition. It was not until Stuhmer, in 1928, called it "balanitis xerotica obliterans," however, that a permanent name was given to the condition.

The etiology is not well defined. The condition is an atrophic one, as contrasted to hypertrophic processes, such as the erythroplasia of Queyrat or leukoplakia. It should also be distinguished from lichen planus, psoriasis, scleroderma, or carcinoma of the penis.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

In 1944, Lehman and Freeman reviewed the literature and reported a total of 24 cases. They found that this particular type of balanitis often was associated with lichen sclerosus et atrophicus elsewhere in the body. Pathologically, biopsy specimens of the penile lesions showed them to be identical with the lesions of lichen sclerosus et atrophicus. The incidence is certainly much larger than that reported in the literature.

This condition may occur spontaneously; it may occur after inflammatory lesions of the penis and glans penis; it has been reported after circumcision, dorsal slit, electrocauterization of the penis, and, in one case, after penile amputation on the stump of the penis. As with other atrophic lesions of the skin, treatment for this condition is completely unsatisfactory and revolves around treatment with various bland ointments to keep the skin moist, and, perhaps, local therapy with various cortisone or cortisone-like ointments. In cases in which the sclerosis has involved the urethral opening, a wedge-type meatotomy may be necessary. Similarly, when there is severe involvement of the prepuce, circumcision may be necessary. Other treatment seems to be useless.

Farrington and associates (*J. Urol.* 73:1054 [June] 1955) reported the use of intravenously given procaine as suggested by Turner for the treatment of scleroderma. This was tried by the author in one case of balanitis sclerotica obliterans, with use of intravenously given procaine in a 1% solution over a period of four or five days, with reported remission of symptoms for a period of one year after treatment. No further reports or long-term follow-up studies have been available in the literature since that time. This is the only new idea in treatment which has been advocated for some time. The possible use of steroids in the control of this condition may offer relief in the extreme case, but, to date, there have been no reports of long-term follow-ups of patients treated by steroid therapy.

POOR CONCENTRATION

To the Editor:—*Please suggest a program to improve concentration in an 8-year-old child who has a short attention span and is unable to concentrate except for short periods. He is of average intelligence, but his attention flits about in school. He loses place in reading class and does not concentrate on any problem at hand. When forced to do so, he can solve any average problem or read well, but when force is withdrawn his attention is immediately attracted to something else.* *H. W. Brabson, M.D., Baden, Pa.*

Answer.—Although this 8-year-old boy has been shown to have good average intelligence by a psychological examination, his problem needs further investigation. His failure in attention is not due to a lack of intelligence and must be considered symptomatic of another condition. In reviewing the differential diagnosis, it is presumed that a complete physical and neurological examination, including hearing and vision, was made and that organic cerebral disease has been ruled out. The possibility of a childhood psychiatric condition must be considered.

A common reason for poor concentration and attention span is anxiety. Frequently not apparent on the surface, it results from unconscious inner conflicts and tensions. Such tensions lead to retreats into fantasy and withdrawal of interest and energy to inner mental activities, which distract from the outside work at hand. Common problems in such instances are parental conflicts, sibling rivalry, overly severe discipline, inconsistent or inadequate discipline, and sexual distractions. The diagnosis is a childhood anxiety neurosis in which the lack of concentration is one symptom in a syndrome with others that can be found by a careful psychiatric examination.

Obviously, precise recommendations cannot be made until the diagnosis and its psychodynamic factors are established. If properly diagnosed, remedial measures can be introduced and the prognosis can be good. If neglected, significant personality retardation and secondary psychiatric complications may arise. Occasionally, however, by timely maturation and learning—referred to in the vernacular as "growing out of it"—the ego is strengthened to move out of the conflict and disturbance, which is then considered a spontaneous improvement.

PENICILLIN USED PROPHYLACTICALLY

To the Editor:—*When was penicillin first used prophylactically against streptococcic infections in patients having chronic glomerular nephritis?* *V. W. Higgins, M.D., Essex, Conn.*

Answer.—The consideration of the possible prophylactic usefulness of penicillin in glomerular nephritis for preventing streptococcic infections stems mainly from studies on the prophylactic efficacy of penicillin against first attacks and recurrences of rheumatic fever by prevention of streptococcic infections. These studies, in turn, stemmed from earlier studies of the relationship between rheumatic fever and hemolytic streptococcic infections and of the usefulness of sulfonamide drugs in preventing recurrences of rheumatic fever. Most of the important references are cited in the Symposium on Rheumatic Fever and Rheumatic Heart Disease in the December 1954 issue of the *American Journal of Medicine.* Less work has been done on the prophylactic use of penicillin in glomerular nephritis. Rammelkamp and associates, in the 1954 issue of the *Transactions of the Association of American Physicians,* reported on the study of an epidemic of glomerular nephritis and presented evidence which suggested that penicillin treatment of hemolytic streptococcic infections lessened the likelihood of occurrence of first attacks of acute glomerular nephritis. However, the experience of this group of investigators as well as of others suggests that glomerular nephritis, unlike rheumatic fever, is likely to follow infection with only certain types of group A hemolytic streptococci, particularly type 12. If this is so, penicillin prophylaxis is likely to have less specific effect in preventing exacerbations of glomerular nephritis, since type-specific immunity to hemolytic streptococcic infections usually persists for some time, making the recurrence of infection with type 12 (and certain other so-called "nephritogenic" strains) unlikely even without prophylactic chemotherapy. While convincing data on the efficacy of prevention of relapses or exacerbations in chronic glomerular nephritis are not available, physicians have used penicillin prophylactically in various ways on the assumption that intercurrent infections, some of which may be prevented by administration of penicillin, may serve as "trigger" rather than specific mechanisms in exacerbations of glomerular nephritis.

HYPERTENSIVE RETINOPATHY

To the Editor:—*Please describe the Keith-Wagener-Barker, Brust-Perera-Wilkins (A. M. A. committee), and Pickering classifications of hypertensive retinopathy.* *M.D., Mexico.*

Answer.—The Keith-Wagener-Barker classification assigns a single general grade to the retinal findings in each patient. It is based on the general clinical status of the patient, not on the eye findings alone. It includes evaluation of cardiac and renal functions and of cerebrovascular and ophthalmic changes. The classification is as follows:

Group 1.: minimal or no changes in all four systems mentioned above. Fundi may show grade 1 arteriolar attenuation and sclerosis. The patient has no symptoms. Group 2.: Moderate-to-marked angiopathy with attenuation and sclerosis, but no retinopathy. Occasionally, however, there may be venous occlusions due to atherosclerosis. Other systems are affected, but function is adequate. Group 3.: angiopathy and retinopathy present, with hemorrhages and exudates. Patients almost always have symptoms. Other systems are definitely affected. Group 4.: ocular signs, as in group 3, plus papilledema. Patients have serious impairment of cardiac or renal functions. Encephalopathy is frequent. Symptoms are severe.

The system recommended by the American Ophthalmological Society's Committee on "Classification of Hypertensive Disease of the Retina" is reputed to be a preferred classification.

Brust, Perera, and Wilkins, acting as an *ad hoc* subcommittee to the A. M. A. Committee on Research, proposed a classification of types of hypertension. Their report (J. A. M. A., 166:640 [Feb. 8] 1958) listed the following types of hypertension: (1) diastolic hypertension, (2) primary hypertension, (3) secondary hypertension, (4) accelerated form of hypertension, and (5) encephalopathy.

Pickering considers that there are only two forms of retinitis in hypertension, one of which is characteristic of malignant hypertension. He designates these as albuminuric retinitis (or hypertensive neuroretinopathy) and arteriosclerotic retinitis (or arteriosclerotic retinopathy).

REACTION TO TETANUS ANTITOXIN

To the Editor:—*A 44-year-old woman received her first injection of poliomyelitis vaccine on July 20, 1959, and her second on Sept. 16, 1959. On Oct. 7, 1959, she cut her finger on a rusty scissors she used for gardening. After having had proper skin tests she was given 1,500 units of tetanus antitoxin and 0.5 cc. of tetanus toxoid. On Oct. 14, 1959, she developed pain in both upper arms, which was severe at the site of the tetanus antitoxin injection. The site of the skin test also showed erythema and tenderness. The next day a rash appeared over most of her body and she had general myalgia and aching joints. She was treated with corticotropin-zinc hydrochloride and other supportive measures. The process remained uncontrolled for three weeks, during which she complained of weakness and was unable to raise her arms. She now has a winged left scapula and atrophy of the musculature of the anatomist's snuffbox of the right hand. If she had concurrently poliomyelitis and an adverse reaction to tetanus antitoxin, is there any correlation with or significance in the proximity of the second poliomyelitis and the tetanus antitoxin injection? Was there a synergistic or potentiated action between the injections, or was the picture of this illness coincidental?*

J. G. Wolf, M.D., Del Mar, Calif.

Answer.—The diagnosis is complicated by the history of isolated paralysis of the left serratus and right interosseus muscles. The usual type of isolated serratus paralysis is related to damage to the long thoracic nerve of Bell resulting from "fibrositis" in the fascial planes of the shoulder, with or without trauma, rather than poliomyelitis. It is likely that some local condition, possibly trauma to the ulnar nerve at the elbow or at the wrist, was the cause of the wasting of the interosseous muscle. However that may be, the patient then developed an acute serum reaction to the tetanus antitoxin. Development of the inability to raise both arms within 7 to 14 days after a serum reaction is typical of a serum neuritis which affects both axillary nerves, and sometimes other branches of the brachial plexus. This is a common complication of a reaction to tetanus antitoxin. In the future, injections of horse serum should be avoided. Since poliomyelitis vaccine does not contain foreign serum, it is blameless in this respect.

URINARY SOLUBILITY OF TOLBUTAMIDE

To the Editor:—*A middle-aged patient with diabetes mellitus and a stag-horn renal calculus was treated for several years with tolbutamide. Since tolbutamide is chemically related to sulfonamide, it is likely to cause crystalluria. If so, would tolbutamide have any detrimental influence during an operation for the removal of the stag-horn calculus?*

Charles T. Buckingham, M.D., Marion, Pa.

Answer.—The solubility of the excretion product of tolbutamide that appears in the urine of patients treated with this drug is stated by the manufacturer to be of the order of 2 Gm. per 100 ml. at pH 5.5. The solubility is much greater in more alkaline mediums. Crystalluria therefore is virtually absent in patients receiving therapeutic doses of tolbutamide, and no appreciable risk need be expected from its use even in the presence of a renal calculus.

Although tolbutamide in and of itself has no detrimental influence during an operation for removal of a urinary calculus, it must be emphasized that this drug alone is often insufficient to control diabetes during and after surgical procedures and should not be relied on for this purpose. Most patients with even mild diabetes require administration of insulin in connection with major operations.

RELATION OF STROKE TO PAST HEAD INJURY

To the Editor:—*What is the longest period that can lapse between the occurrence of a minor head injury (without fracture or concussion) and the development of a cerebral thrombosis? The question concerns an employee who received such an injury five years prior to having a stroke. Although he lost no time from employment through those years, an attempt is being made to claim that the stroke was the result of the old injury.*

M.D., California.

Answer.—No causal relationship has been established between minor trauma to the head not productive of fracture, cerebral contusion, or direct injury to the cervical portion of the carotid arteries, and the subsequent development of thrombosis of intracranial arteries. Head injury of such severity as to fracture the sphenoid bone may traumatize the carotid artery in its course through the foramen lacerum and in the cavernous sinus, and lead to thrombotic occlusion. Direct trauma to the cervical portion of the carotid artery may have a similar result. Fracture dislocations and other injuries of the cervical spine may occlude a vertebral artery. Head injury of sufficient severity to produce cerebral contusion and laceration may be followed by the delayed appearance, one week to one month or more later, of so-called "delayed traumatic apoplexy," which most often proves to be due to an intracerebral hematoma. Occasionally, a patient with a minor head injury associated with injury to other parts of the body accompanied by shock may develop cerebral thrombosis originating at the site of an already present atheromatous plaque. Since none of these circumstances existed in the case in question, the minor injury experienced five years prior to the development of cerebral thrombosis must be considered innocent of any connection with the later development.

CHILDHOOD DERMATITIS AND STEROID THERAPY

To the Editor:—*A 7-year-old boy has severe allergic dermatitis. He has had skin tests and is avoiding the antigens to which he is sensitive. It was necessary to give 2 mg. of triamcinolone daily to control the rash. Is there any danger associated with the continued use of this drug?*

R. S. Srigley, M.D., Altus, Okla.

Answer.—The administration of 2 mg. of triamcinolone daily for a period of a few weeks or several months should not arrest growth in a 7-year-old child. This medication should not be continued indefinitely, however. Perhaps the administration of antihistamines, general measures, and adequate local treatment should lessen the necessity of resorting to corticosteroids and certainly should make it possible to decrease the dose slowly. The help of a competent dermatologist is indicated. The presence of an associated dermatitis which is not allergic should be ruled out. Vitamins should be supplied. The danger in most of these cases is from overtreatment with local agents.

RACIAL ORIGIN AND DISEASE

To the Editor:—*Frequently medical histories start with information about the patient's belief that his color usually makes no definite contribution to solving the problem of the illness. In which diseases does skin color contribute to making the diagnosis and determining the type of treatment?*

William H. Brown, M.D., Elizabeth, N. J.

Answer.—The terms white and colored are too nonspecific to be useful in a medical history. Words and phrases which provide a clearer picture of the patient's racial origins and background should be used, such as Caucasian, Slavic, Greek, Jewish, Negro, Chinese, or East Indian. These more specific designations provide evidence concerning genetic factors and environmental exposure which do influence the incidence and course of disease. A few of the many diseases which exhibit a predilection for a specific racial group are sickle cell anemia, in Negroes; Tay-Sachs disease, in Jews; Cooley's anemia, in persons of Mediterranean origin; nasopharyngeal carcinoma, in Chinese; keloids, in Negroes; fibromyomas, in Negroes; polydactylism, in Negroes; and umbilical hernia, in Negroes.

Some racial groups show a low incidence of certain diseases such as basal cell carcinoma, in Negroes; malignant melanoma, in Negroes; carcinoma of the uterine cervix, in Jews; carcinoma of the penis, in Jews; and endometriosis, in Negroes.

The examples cited above are just a few selected at random from what could be a lengthy list and dissertation. It is not a person's skin color but his racial origins which contribute significantly to making a diagnosis and determining treatment.

DERMATOSIS FROM SUNLIGHT

To the Editor:—*A young woman develops a dermatitis on her arms and legs when exposed to the sun. It is a problem for her, since she is a receptionist. What treatments will give the best results?* *David A. Bagley, M.D., Austell, Ga.*

Answer.—In some patients eruptions due to hypersensitivity to light are precipitated by ingested drugs (sulfonamides, chlorpromazine, chlorothiazide, certain orally given antidiabetic agents, acetazolamide, and others); in that event such drugs must be strictly avoided, but in most cases of eruptions due to sunlight no specific cause or underlying systemic disease can be found. If the patient in question belongs to this group, the following measures can be tried: strict avoidance of exposure not only to direct and reflected sunlight, but also to sunlight which has passed through window glass; wearing of clothing which helps to shield against sunlight (hats, long-sleeved dresses, gloves, and heavy stockings); applications of "sunprotective" lotions, creams, or ointments; and administration by mouth of antimalarial agents, e. g., chloroquine, 250 mg. one to three times daily, or hydroxychloroquine sulfate, 200 mg. one to four times daily.

IRRADIATION OF TONSILLAR LYMPHOID TISSUE

To the Editor:—*Does radiation to the eustachian tube, the nasopharynx, or both, for hypertrophic lymphoid tissue endanger the patient's welfare in any manner?*

Robert B. Robertson, M.D., Red Bank, N. J.

Answer.—To answer this question categorically one would have to belong to that group of which it could be said, as Justice Holmes said of the Supreme Court, that they are "often in error, but never in doubt." The answer is simply not at hand. Until it is, one must adopt some sensible "philosophy of risk." One can neither live nor practice medicine without hazard. In my opinion, the risk in this instance is small and the treatment mentioned should be used, provided there is a sound indication for it as, for example, the restoration of hearing in young children when more conservative means have failed.

Answer.—Radiation therapy properly applied to the eustachian tube, nasal pharynx, or both for hypertrophic lymphoid tissue does not apparently endanger the patient's welfare in any manner. This answer is based on the use of properly applied radiation in indicated cases over about 15 years of medical experience.

SITE OF SMALLPOX VACCINATION

To the Editor:—*I remember reading that in certain areas of the world, smallpox vaccination is administered on the sole of the foot of infants not old enough to walk. Is there any objection to this practice? It seems it would be a better place than the thigh or inner surface of the upper part of the arm.* *Robert R. Haumeder, M.D., Pleasant Hill, Calif.*

Answer.—The outer surface of the left arm, at the insertion of the deltoid, is usually the preferred site for vaccination and, on the basis of extensive experience, has been found to be most satisfactory. Vaccination should not be administered on the foot, since inflammatory reaction and scarring in this area, especially if associated with secondary infection, could result in avoidable injury and possibly permanent disability.

OCCUPATIONAL VERTIGO

To the Editor:—*A 29-year-old man works on the production line of a factory. He complains of a sensation of movement of objects around him, which makes him nauseous, tense, and nervous. He is married and has three children. He continues this type of work because the job pays well, and he wants to work there until he has enough capital to go into business for himself. He is a captain in the National Guard Unit and is an intelligent young man. His physical condition is entirely normal. Can the hypnotic effect from the moving objects on the production line, the dull, repetitive work, and lack of incentive for this type of work cause his symptoms?*

Russell S. Pelton, M.D., Ripon, Wis.

Answer.—This man should be examined by a qualified otologist. Audiograms and caloric studies would identify any disturbance of the auditory or vestibular peripheral apparatuses. An electroencephalogram might be helpful in identifying a possible temporal lobe disturbance. When these studies have been completed and assuming his neurological status is normal, everything necessary to exclude a significant organic lesion will have been done, for the time being. Even if the results of these tests are normal, the patient should be seen at regular intervals, if his symptoms persist or progress. In the meantime, the symptoms seem due to specific visual sensitivity to movement, as experienced in the patient's work. Equally possible, as the questioner indicates, is that the symptoms are due to functional causes related to boredom and lack of interest in this type of work.

NARCOTICS ADDICTION AND PREGNANCY

To the Editor:—*A few hours after a baby was delivered from a woman who was a severe heroin (diacetylmorphine) addict, the infant had withdrawal symptoms. The baby was placed for adoption, and presumably the foster parents will know nothing of the mother's addiction. I understand that in morphine and heroin addicts, even when the addiction has been broken for a number of years, a single injection of morphine or heroin may reestablish the habit. Is there a danger that a single injection of morphine given to the child in later life, by a physician having no knowledge of the mother's history, may inadvertently establish an addiction in the child?*

Meyer Zeiler, M.D., Inglewood, Calif.

Answer.—The reestablishment of addiction in the adult by a single injection of morphine or heroin after abstinence for several years is conceivable. The adult has had the previous experiences of adverse moral, social, emotional, and physical reactions to the drug which could be rekindled. In the newborn infant, however, this does not apply. Furthermore, withdrawal symptoms in a newborn infant indicate not addiction but a reaction to removal of the narcotic received transplacentally. In the case of such an infant the inadvertent administration of a single dose of morphine or heroin several years later would almost certainly not establish addiction.

TUBE FEEDING

To the Editor:—*What is the best treatment for difficulty in swallowing in a patient with a pseudo-bulbar palsy which has resulted from bilateral strokes? If the patient can swallow a little, but occasionally aspirates, would a tracheotomy be preferable to a gastrostomy to prevent aspiration and permit normal ingestion of food?*

M.D., Pennsylvania.

Answer.—A tracheotomy in this patient would be of some help in preventing aspiration, but would not completely prevent it. For this procedure to be of benefit, a nurse would have to be available with a suction apparatus to aspirate the trachea, because of the patient's weakness and inability to cough. In view of the patient's weakened condition, a tracheotomy would therefore not be advisable unless the patient is hospitalized. A gastrostomy would not lessen the chance of aspiration significantly, because regurgitation would still be possible whether the food is put into the stomach through a nasal tube or gastrostomy tube. If there is any evidence of ulceration of the esophagus (especially into the larynx) due to the tube, a gastrostomy would then be strongly indicated. Use of a small, soft, plastic tube minimizes the danger of ulceration. Accordingly, neither tracheostomy nor gastrostomy is strongly indicated. More important is the necessity of feeding by the drip method (day and night), which would tend to minimize the collection of large quantities of food in the stomach with vomiting.

SMALLPOX VACCINATION AND CHICKENPOX

To the Editor:—*Can smallpox vaccination in child with chickenpox produce ill-effects? Chicl enpox is endemic in Indiana from November t March. Should smallpox vaccination be withhel during these months?*

M.D., Indiana.

Answer.—Occasionally, chickenpox lesions can b accidentally contaminated by a vaccination, bu generalized vaccinia is not a complication of chick enpox in this situation. Because of the occasiona occurrence of self-inoculated lesions, immune gam ma globulin has been used in this situation in 1 instances without subsequent complications of vac cination. The decision whether to use immun gamma globulin in this situation must be made o the basis of the severity of the chickenpox eruption Vaccination need not be withheld in the face of possible epidemic of chickenpox.

FOLLICULAR LYMPHOBLASTOMA

To the Editor:—*A 54-year-old woman had an exploratory operation which revealed a penetrating ulcer of the duodenum. A biopsy specimen gave the diagnosis of follicular lymphoblastoma. The patient's first gastroenterostomy did not function, and a second operation was performed with success. A biopsy specimen taken at the second operation again revealed Brill-Symmer's disease. What is the treatment for this disease?*

Milton Ende, M.D., Petersburg, Va.

Answer.—It is assumed that the only apparent site of lymphomatous involvement was in the region of the duodenum and that this was surgically removed. It is also assumed that no adenopathy was found within the abdomen and that the spleen and liver were not involved. There apparently were no systemic manifestations of this disease. Many patients having focal involvement of the gastrointestinal tract with malignant lymphomatous disease have a reasonably good prognosis. The best treatment includes complete surgical removal, followed by radiation therapy. Irradiation would be preferable to nitrogen mustard therapy in this instance, since lesions of giant follicular lymphoma usually are radiosensitive. Combined treatment with surgery and irradiation is preferable to surgery alone. The use of nitrogen mustard is ordinarily reserved for patients with marked systemic reaction or in situations where radiation edema might be feared. In general, radiation-induced remissions last longer than those after nitrogen mustard therapy.

EXTERNAL EAR CANAL INFECTION

To the Editor:—*The report on a culture specimen of an infection located in the right external auditory canal was "yeast-like organisms." This infection has existed several years and is resistant to antibiotic therapy. What should the treatment be?*

W. O. Bailey, M.D., Washington, D. C.

Answer.—The treatment of infections of the external auditory canal may be difficult. Most are mixed bacterial infections, and often the skin of the ear canal has become sensitized, hence the term "eczematoid dermatitis"; therefore, antibiotics combined with a steroid applied topically usually give the best results. It is important that the canals be thoroughly cleansed of exudate and epithelial debris before the drugs are applied topically.

Sometimes fungous infections are responsible for external otitis (otomycosis). The antibiotics usually promote, rather than inhibit, the molds, especially if the topical antibiotic preparation contains a steroid. The preferable general treatment for fungous and yeast-like infections is, again, careful cleansing of the ear canals, preferably by dry methods, and periodic topical application of a fungicide or 2% salicylic acid in 70% alcohol. Periodic cleansing of the ear canal every two or three days, usually for one to two weeks, is sufficient. If a secondary bacterial infection also is present, antibiotics given systemically are helpful.

HEREDITARY LEPTOCYTOSIS

To the Editor:—*What is the treatment of hereditary leptocytosis (Cooley's anemia)? Of what significance is enlargement of the liver in a patient with a hemoglobin level of 8 Gm. per 100 cc.?*

Eugene L. Childers, M.D., Nixon, N. J.

Answer.—There is no specific therapy for hereditary leptocytosis, which is a disease in which the patient has a genetic defect in the formation of hemoglobin. Red blood cell production continues unimpaired and at high levels, but insufficient hemoglobin is produced for the developing red blood cells, which become thin and otherwise deformed. A hemolytic component develops in severe cases, presumably because the spleen destroys some of the small abnormal red blood cells. If hemolysis is greatly increased and numerous transfusions are required, splenectomy may be beneficial (Smith and others, *Blood* 15:197 [Feb.] 1960) in reducing the transfusion requirement and perhaps prolonging life. Transfusions add iron to the tissues, which are already overloaded with iron because it cannot be fully utilized by the developing red blood cell. The liver becomes enlarged, partly because of hemosiderosis, partly because of myeloid metaplasia, and at times because of some degree of cardiac decompensation.

OSTEITIS DEFORMANS AND BACK PAIN

To the Editor:—*A 42-year-old man suffered what appeared to be a bilateral Bell's palsy. He was hospitalized for study, and roentgenograms of his skull and the left iliac bone showed evidence of advanced osteitis deformans (Paget's disease). Recently, when trying to move a table, he had severe pain over the low back, which was treated with adhesive strapping and bed rest. He is now up and moving around on crutches and wears a sacroiliac belt, which makes him more cofortable. What is the latest treatment for osteitis deformans?*

S. B. Kaufmann, M.D., Fall River, Mass.

Answer.—There is no known specific effective treatment of osteitis deformans. This patient's low back pain is possibly due to ligamentous strain at a bony attachment which has been weakened by involvement with osteitis deformans. If so, the usual treatment of ligamentous back strain should prove effective. This should include two or three weeks of protection, including bed rest on a firm mattress, followed by gradual remobilization. Attention should be paid to factors likely to produce recurrence, such as obesity, increased lordosis, and muscular insufficiency.

STERILIZATION OF METAL SURFACES

To the Editor:—*Is there a practical way to sterilize the exterior surfaces of a gas anesthesia machine (including tanks and carriage) after it has been used on a patient with a wound infected by staphylococci? Do ultraviolet rays have sterilizing action if the source is located about 9 ft. from the floor?*

M.D., Ohio.

Answer.—Equipment such as an anesthesia apparatus or a portable x-ray machine can be disinfected by spraying with isopropyl alcohol, 63 oz. (U. S. P.); benzalkonium chloride, in a 12.8% concentration, 1 oz.; and distilled water, 63 oz. An electric paint sprayer is a convenient tool for this purpose and stimulates personnel to do a good job. Thorough wiping of the equipment with a cloth dampened with the germicide is also effective. Germicides packaged in aerosol cans are commercially available. Operating room furniture and litters are easily disinfected by cleaning with a steam jet. Ultraviolet radiation sterilizes air-borne bacteria in dust-free air. It has little effect on surfaces or liquids, from which much of the radiation is reflected. Ultraviolet light has no effect unless there is direct exposure; hence, bacteria in the shadow of dust and dirt on dark surfaces escape destruction.

POLYURETHANE PLASTIC FOAM FOR FRACTURES

To THE EDITOR:—*In a reply in Questions and Answers in* THE JOURNAL, *Feb. 27, page 992, the use of polyurethane plastic foam in the treatment of fractures is recommended. I have just finished an investigation on polyurethane plastic, including foam. Here is a brief summary of my paper dealing with the carcinogenic action of polyurethane foam in animals.*

In connection with testing of a series of water-insoluble polymers for carcinogenic properties, it was found that polyurethane foam, when implanted either as a sponge or as a powder into the abdominal cavity of rats, produced not only sarcomas but also adenocarcinomas of the cecal mucosa at the sites where the polymer was in contact with, and became adherent to, the intestinal wall. Since polyurethane plastics have been used in cosmetic and orthopedic surgery during recent years, these observations are of distinct scientific and practical importance.

The carcinomas of the cecum were found as early as 10 months after implantation of the sponge. They extended retroperitoneally from this organ into the region of the lower pelvis. They were gelatinous adenocarcinomas, with the exception of one which was a rather anaplastic adenocarcinoma. The stroma of some of these tumors contained foreign body granulomas in which clear flakes of the implanted plastic were located in small cysts surrounded by multinucleated flattened giant cells. In a few of these tumors, osteoid and osseous tissue was present in the stroma. The single abdominal sarcoma found in one of these rats with intra-abdominal implants of polyurethane foam was a bone-forming osteogenic sarcoma attached to the right abdominal wall. The sarcoma at the nape of the neck was an anaplastic giant cell sarcoma. The nape of the neck was also the site of foreign body granulomas containing fragments of the implanted plastic. It was evident from the histological evidence that the plastic was being acted on by the cells of the body.

The carcinogenic action mechanism is evidently a chemical one, since the foam was destroyed by the surrounding connective tissue and, in some instances, was not any longer demonstrable. The evidence thus suggests that not only polycyclic aromatic hydrocarbons and aromatic amines but also carbamate derivatives may elicit, without the aid of cocarcinogens, carcinomas and sarcomas under proper experimental conditions. These observations should caution against indiscriminate parenteral use of polyurethane plastics in medical practice and provide an indication for comprehensive testing of these and other polymers for possible carcinogenic effects from their oral introduction (Berenblum and Haran-Ghera).

The use of this particular plastic, as well as many others, has been recommended and adopted by the medical profession without the proper, previous, long-term investigations on possible carcinogenic sequelae resulting from the use of such substances. It would be deplorable if, as a result of such practices, we would in coming years have to face a repetition of the sad story of sarcomas and carcinomas developing after parenteral administration of thorium dioxide solutions for diagnostic purposes.

W. C. Hueper, M.D., Chief
Environmental Cancer Section
National Cancer Institute
Bethesda 14, Maryland.

To THE EDITOR:—*I have read your reply to the letter of the M.D. from New Mexico, J. A. M. A., Feb. 27, page 992. The answer to the first part of the question is correct. The answer to the second part is misleading, and too much space is given to Ostamer. Furthermore, when you are considering local surgical treatment to enhance formation of bony callus, the time-honored and tested methods are as follows: (1) continuous, uninterrupted immobilization in plaster, (2) contact compression by methods of either internal or external fixation systems, (3) inlay bone grafts with fresh autogenous bone, and (4) intramedullary fixation without exposure of the fracture site, or with external implantation of fresh autogenous bone. When dealing with the problem of the individual bone it is important to realize that the rate of healing is extremely variable from one site to another in the skeleton. To specifically answer such a question by mail, it is necessary for the doctor to specify the name of the bone and the location of the fracture. These considerations are as basic in orthopedic surgery as those of the pulse and blood pressure are to internal medicine.*

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WASHINGTON NEWS

Retirement Plan for Physicians . .
Health Care Legislation . .
Licensing of Polio Vaccine Indefinite . .
Miscellany . .

COMMITTEE APPROVES TAX RELIEF FOR SELF-EMPLOYED

The Senate Finance Committee approved by a 12 to 5 vote a modified House-passed bill that would give major tax relief to physicians and other self-employed persons on income set aside for retirement.

The major change in the House bill (H. R. 10) would oblige self-retired persons to set up retirement plans for their employees before they could take advantage of the measure themselves. However, physicians would have three years to establish the retirement plans for their employees.

Before the Committee voted on the measure, Dr. F. J. L. Blasingame, Executive Vice-president of the American Medical Association, advised it that the A. M. A. did not object to inclusion of employees in retirement programs established by or for the self-employed.

This modification was the most significant of the revisions which the Treasury sought.

In its present form, the measure would permit physicians and other self-employed persons to defer taxes on 10% a year of earned income, or $2,500, whichever is smaller, set aside in retirement plans. The deduction could be taken each year for 20 years for a maximum of $50,000.

Taxes on this income would not be due until the person retired and started drawing from the retirement fund. The person then would probably be in a lower tax bracket, and the taxes would be less than if paid at the time the income was earned.

The tax deferral privilege would become effective for self-employed persons on Jan. 1, 1961.

The Treasury estimated the Finance Committee's version would result in an annual revenue loss of between $150 million and $250 million, compared with the estimated $365 million price tag on the House bill.

As urged by the Treasury, the Senate Committee bill also would cover existing pension plans of corporations when the manager is also the owner.

The House version would permit the self-employed to include investment income in the tax-deferral program. But the Finance Committee agreed to the Treasury recommendation that the plan be limited to earned income in most instances.

The Senate Committee also concurred with another Treasury recommendation in eliminating a provision of the House bill that would permit persons over 50 years of age to postpone taxes each year on more than the limits of 10% of income or $2,500 annually.

The Finance Committee's version of the legislation was given about a 50-50 chance of being approved by the Senate. If approved by the Senate, the final version of the measure would have to be ironed out in a House-Senate Conference Committee.

Acceptance of most of the Treasury recommendations was believed to have removed the threat of a veto by President Eisenhower should Congress pass the legislation.

AGED HEALTH PLAN ADVANCES IN HOUSE

By stamping final approval on a catchall Social Security revision bill, the House Ways and Means Committee gave a legislative push to a federal-state plan to provide free health care for an estimated 500,000 to 1,000,000 aged persons with limited incomes.

Rep. Wilbur D. Mills (D., Ark.), the Committee's chairman who developed the plan for health care of the aged, introduced the legislation in the House a week after the Committee had tentatively approved it.

The measure, which also would extend Social Security coverage to physicians, became H. R. 12,580.

Before formally approving the legislation, the Committee rejected, by a lopsided vote, a plea from pro-labor Democratic members that the House be given a chance to also vote on Forand-type legislation that would use the Socital Security system to provide health care for the aged.

Instead, a majority of the Committee voted to ask the House Rules Committee to clear the measure for floor action under a "no amendment" procedure.

However, supporters of Forand-type legislation said they would renew their fight when the legislation reached the Senate even if the House did not have an opportunity to vote on the Social Security approach.

Although the Mills plan was included in the omnibus bill of Social Security revisions, it would not utilize the Social Security setup in either administration or financing.

The Council of State Chambers of Commerce concluded after a study of six medical care plans pending in Congress that the Mills bill is "the least compulsory, the least costly and the least political." But the Council said that even the Mills bill amounted to "another big step" toward assumption by government of individual, family, church, and community responsibilities.

A health-care-for-the-aged measure introduced by Sen. George Smathers (D., Fla.) would give income tax credits to private insurance firms having losses on special low-cost health insurance for persons over 65 years of age. It also would give full

(Continued on next page)

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federal income tax deductions for medical expenses to persons with annual income of less than $5,000. Persons with higher incomes would be granted partial, sliding-scale, deductions.

Although he did not immediately put it in legislative form, Senate Democratic Leader Lyndon B. Johnson of Texas proposed a plan of matching contributions—0.5 of 1% each from employers and employees—to be put in a special fund to finance medical expenses of the workers after age 65.

Without being specific, Johnson predicted that Congress would approve some medical care program for the aged before adjournment.

LIVE VIRUS POLIO VACCINE

Dr. Leroy E. Burney, Surgeon General of the Public Health Service, said that it still is too early to license a live virus vaccine against polio.

He said in a statement that the PHS takes "very seriously" its responsibility of making sure that such a vaccine is safe and effective before it is licensed.

"When the technical experts of the National Institutes of Health and their highly competent advisers are satisfied on these two points, it will be possible to license a live polio vaccine but not before," Dr. Burney said. "How soon that will be, I do not know."

Dr. Burney made the statement in commenting on the Second International Conference on Poliomyelitis held here under auspices of the World Health Organization. He said that reports made at the conference showed that a tremendous amount of work on live virus polio vaccine had been carried out in the past year.

He asked the PHS Technical Advisory Committee on Poliomyelitis to immediately start a careful study and analysis of the voluminous material presented at the conference "to see whether or not the studies presented have provided adequate answers to the questions of changing virulence, potency and effectiveness."

However, the PHS Division of Biologics Standards already is working with live virus vaccin manufacturers to develop production controls tha will asurre a safe, standardized, product.

To date, he said, only one manufacturer—who was not named—has applied for a license. The request was returned for additional information, and no applications now are pending.

PHS technical experts and scientific advisers are not yet convinced that all of the technical problems have been resolved in the development of a successful live virus vaccine against polio, he said.

"Among them are the significance of the changes which have been noted in the virulence of strains isolated after successive human passages, the effectiveness of the vaccines, and firm dosage recommendations which would include the best method of administering the three types of live vaccine," Dr. Burney said.

Dr. Burney urged that, until an orally administered vaccine is licensed, full use be made of the Salk vaccine which he termed "a proved and highly effective means for fighting polio." He noted that it had been administered to about 80 million Americans during the past five years.

"And, despite a high polio incidence in the summer of 1959, it has proved over 90% effective when

(Continued on page 31)

the recommended course of injections is followed," he said.

Use of live vaccines in the United States now are limited to carefully controlled field studies, such as the one in Dade county (Miami), Fla.

Dr. David E. Price, Assistant Surgeon General of the PHS and Chief of the U. S. delegation at a polio meeting in Moscow last month, reported that pieces of candy containing Russian-produced Sabin vaccine had been given to 60 million Russians, aged 2 months to 20 years.

"Russian physicians said that they were encouraged to hope that this method would completely control the disease in Russia within the next year or two," Dr. Price said. "They agreed, however, that further studies of the effectiveness and duration of effectiveness were needed."

A summary of findings of the International Conference in Washington also said longer observation of results is needed because of "the low attack rate of paralytic diseases and the well-known variability of occurrence of poliomyelitis from one period of time to another in the same community.

MISCELLANY

The House Commerce Committee approved legislation authorizing a stepped-up program of international medical research, with this government using counterpart funds abroad to finance its activities. The Senate last year approved a bill calling for a 50 million dollar annual program financed from general revenues.

The administration asked Congress to allow it to reshuffle the present Hill-Burton program of aid for hospital construction, without adding any more money to the program, in order to: (1) permit and encourage states to give more attention and, in exceptional cases, higher priority to projects for the modernization of hospitals and public health centers; (2) authorize increased federal participation in research and experimentation for more effective use of the services and resources of hospitals and other medical care facilities; (3) place greater emphasis on the construction of special facilities for the care of long-term patients by consolidating the two present categories of chronic disease hospitals and nursing homes; (4) liberalize conditions under which the construction of mental health clinics, or in certain areas, general medical care clinics may be eligible for aid under the program, and (5) make available grants to regional, area, and local planning groups to coordinate the planning of hospitals and other medical facilities and services.

In addition, the administration proposed to establish a program of federal guarantees of bonds of private group practice agencies or organizations to assist them in financing group practice medical or dental care facilities. Under this program, the surgeon general would be authorized to guarantee payment of the debt service on bonds sold by group practice agencies or organizations, and payable in 30 years or less. The guarantee would cover debt service on such bonds to the extent that the pledged revenues prove inadequate. The aggregate amount of such guaranteed bonds outstanding at any one time would be set in appropriation acts, but in any event would not be in excess of 30 million dollars. No new contract could be entered into after June 30, 1965.

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EXPERIMENTAL VACCINATION AGAINST MEASLES

I. TESTS OF LIVE MEASLES AND DISTEMPER VACCINE IN MONKEYS AND TWO HUMAN VOLUNTEERS UNDER LABORATORY CONDITIONS

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and
Charles J. York, Ph.D., Indianapolis

The antigenicity and safety of modified live virus measles vaccine was studied in monkeys and in two children. None of the monkeys inoculated orally, intramuscularly, or intercerebrally showed signs of disease, and all produced antibodies. Two children inoculated with the vaccine had a good immunologic response but developed a mild illness with fever, sore throat, and some leukopenia. Distemper virus, believed to be antigenically related to measles virus, was also tested by intramuscular and intercerebral inoculation into susceptible monkeys. No signs of illness were observed, and all monkeys tested developed antibodies against distemper. None produced measles-neutralizing antibodies even after two injections of distemper virus. It would appear that the strain of distemper virus used in these experiments lacked the antigenic component which would cause significant measles antibody production.

Measles is one of the most infective exanthemas known to man and represents an important health problem because of its high morbidity. In countries such as the United States, the virus is widely disseminated and endemic in the population and is, therefore, chiefly a pediatric problem. In more isolated areas of the world, however, this disease may constitute a serious problem to whole populations, as shown only recently in the case of the measles epidemics in Greenland, described by Christensen and co-workers,[1] and in Panama, as will be discussed in the second paper. With the exception of gamma globulin, which is limited in its usefulness, there is no effective means of protecting susceptible populations against this disease at the present time.

Two scientific advances in the field of virology have, however, laid the foundation for a rational approach to vaccination against measles. The isolation of measles virus in tissue culture by Enders and Peebles[2] in 1954, and the adaptation of this virus to different tissue culture systems such as chick embryo[3] made possible the development of a measles vaccine. Enders and co-workers[4] and Katz and Enders[5] demonstrated that the Edmonston strain of measles virus, after a series of passages through human kidney–tissue culture, human amnion–tissue culture, embryonated eggs, and chick embryo–tissue culture produced no disease when inoculated into monkeys and only mild disease in susceptible children, with significant development of measles antibodies.

A second approach to the problem of measles prevention was opened up when Pinkerton and co-workers[6] as well as Adams and co-workers[7]

From the Research Division, Pitman-Moore Company.

suggested a relationship between canine distemper and measles on the basis of common clinical and pathological features. Carlstrom,[8] in Sweden, and Adams and Imagawa[9] in the United States, demonstrated an immunologic relationship between these two viruses. The feasibility of using distemper virus inoculations to provide protection against measles was suggested by this relationship and was further substantiated by the findings of Adams and co-workers[10] that a three-fold reduction in measles incidence occurred in subjects receiving distemper vaccine, compared with three control groups.

This paper reports the results obtained by inoculating monkeys and two human volunteers with a modified live measles vaccine prepared in chick embryo-tissue culture. It also elucidates the immunologic relationship between distemper and measles viruses as tested in monkeys. The safety and efficacy of both live vaccines in a larger number of human subjects are elaborated on in the second paper published in this issue.

Preparation of Tissue Cultures, Virus, and Vaccine and Test Procedures

Chick Embryo Tissue Culture (CETC).—CETC was prepared by mincing 8-to-10-day-old embryos after removal of the eyes, washing them with phosphate-buffered saline solution, and trypsinizing them in the conventional manner in an Erlenmeyer flask agitated with a magnetic stirrer. After centrifugation at 1,000 rpm for three minutes, 500,000 to 600,000 cells per milliliter were suspended in growth medium consisting of 5.0% calf serum and 0.5% lactalbumin hydrolysate in Earle's basic salt solution containing 200 units of penicillin and 200 mcg. of streptomycin per milliliter. This mixture was then inoculated in amounts of 1 ml. into roller tubes and in amounts of 60 to 70 ml. into Blake or Roux culture flasks. The medium was removed after 24 to 48 hours, the cells washed twice with medium 199 to remove any serum remaining from the growth medium, and 2 ml. of medium 199 without serum and a pH of 7.0 to 7.2 was added to each tube, or 100 ml. to each flask. Cultures were then ready for inoculation with virus.

Human Heart Tissue Cells (Girardi) (HHTC).—HHTC were used as an indicator of virus in titration and identification tests. Two hundred thousand to 500,000 cells per milliliter in Eagle's basal medium (EBM) plus 10% calf serum were dispensed into culture tubes. Regular medium changes were performed at intervals of three to four days with EBM plus 2% calf serum.

Human Amnion Tissue Culture (HATC).—HATC was prepared according to the method of Zitcer and co-workers.[11] Three hundred thousand to 500,000 cells in 1 ml. of Eagle's basal medium plus 10% calf serum were dispensed into culture tubes. The medium was changed about every seven days.

Measles Virus.—The Edmonston strain of measles virus used for this study was obtained from Enders. This virus had been propagated 24 times in human kidney tissue culture, 28 times in human amnion tissue culture, 6 times in embryonated eggs, and 13 times in chick embryo tissue culture (CETC) in Enders' laboratory. After four additional passages in CETC in our laboratory, series of virus pools were prepared for the following experiments.

Distemper Virus.—The distemper virus was obtained from the Cornell Virus Research laboratories as the 43rd passage of the egg-adapted strain originally isolated by Cabasso and Cox.[12] This virus was passed about 37 additional times on the chorioallantoic membrane (CAM) of 8-day-old embryonated eggs before use in these studies. In the first monkey experiment, a 10% suspension of infected CAM was injected. All subsequent experiments were performed with distemper virus propagated in CETC.

Vaccine Preparation.—Measles vaccine and distemper vaccine in CETC were prepared in the same manner, except that the inoculum for the measles vaccine preparation was 2.5 to 5.0 ml. of virus per bottle and for distemper vaccine 1.0 ml. per bottle. In both cases, virus was harvested with one freezing and thawing when 50 to 100% of the cells exhibited a cytopathogenic effect (CPE). The cell debris was then removed from the infected tissue culture fluid by centrifugation at 1,000 rpm for 10 minutes. Equal amounts of supernatant and an appropriate stabilizer were mixed and filled in vials. The material was either lyophilized or stored frozen at −70 C (−126 F). Titers of different batches of measles vaccine ranged from $10^{2.5}$ to $10^{4.5}$ tissue culture infective doses 50% ($TCID_{50}$) per 0.2 ml. Different pools of distemper vaccine had titers ranging from $10^{3.0}$ to $10^{4.5}$ egg-infective doses 50% (EID_{50}) per 0.1 ml. The exact amount of virus inoculated in each instance is given in the appropriate tables. The identity of these viruses was established by neutralization tests with specific immune serums. Safety and sterility tests on the final pools consisted of inoculation of 1 ml. of vaccine into 600 ml. of thioglycollate in triplicate and of interperitoneal and subcutaneous inoculations of guinea pigs and mice. None of these tests showed any detectable micro-organisms. Each vaccine pool was also tested by intramuscular and intracerebral inoculation of cynomolgus monkeys prior to use in human beings. Measles antibody response was measured by the complement-fixation and neutralization tests. Distemper antibodies were determined by neutralization tests in embryonated eggs.

Complement-Fixation Test for Measles Antibodies.—Tissue culture fluid from measles-infected human amnion tissue culture (HATC), inactivated at 56 C (132.8 F) for 30 minutes, was used as antigen. Control antigens from noninfected HATC were included in each test. Two units each of complement, antigen, and hemolysin plus 2% sheep cells, each in amounts of 0.2 ml., were used in the test. Serums inactivated twice at 56 C for 30 minutes were used in twofold dilutions. Complement fixation was carried out at 4 C (39.2 F) overnight, after which the hemolytic system was added, with incubation at 37 C (98.6 F) for 30 minutes. Endpoints were determined at 50% fixation of complement.

Table 1.—*Results of Oral Inoculation of Live Measles Vaccine into Cynomolgus Monkeys*

No. of Monkeys	Inoculum $TCID_{50}$	Virus Recovery*		Preinoculation and Postinoculation Antibody Response			
				Complement-Fixing		Neutralizing	
		Blood	Throat	Before	After†	Before	After†
2 (controls)	Normal tissue culture fluid	0/2	0/2	0/2	0/2	0/2	0/2
1 (cage contact)	...	0/1	0/1	0/1	0/1	0/1	0/1
1 (room contact)	...	0/1	0/1	0/1	0/1	0/1	0/1
4	$10^{4.5}$	2/4	3/4	0/4	4/4‡	0/4	4/4§

* Number responding = numerator; denominator = number tested.
† 6 weeks after inoculation.
‡ Range of complement-fixing antibody, 1:128 to 1:512.
§ Range of neutralizing antibody, 1:32 to 1:320.

Measles Neutralization Test.—A mixture of equal amounts of serum, or serum dilutions, and equal amounts of virus in a final concentration of about 100 $TCID_{50}$ was incubated for one hour at room temperature and 0.2 ml. was inoculated into each of several culture tubes. The final reading was recorded when about 100 $TCID_{50}$ was present in the simultaneous virus control titrations.

Distemper Neutralization Test.—A mixture of equal amounts of serum, or serum dilutions, and equal amounts of virus in a final concentration of about 100 egg-infective doses 50% (EID_{50}) was incubated at 4 C (39.2 F) overnight and 0.1 ml. of this mixture was inoculated into the chorioallantoic membrane (CAM) of each of four to six 8-day-old embryonated hens' eggs. A simultaneous titration of the virus was performed. After incubation for six days at 35 C (95 F) the eggs were opened, the CAM was removed, and they were observed for typical lesions. Two or more lesions on the CAM indicated that the virus was not neutralized by the serum.

Table 2.—*Results of Intramuscular Inoculation of Live Measles Vaccine into Cynomolgus Monkeys*

No. of Monkeys	Inoculum $TCID_{50}$	Virus Recovery*		Preinoculation and Postinoculation Antibody Response			
				Complement-Fixing		Neutralizing	
		Blood	Throat	Before	After†	Before	After†
2 (controls)	Normal tissue culture fluid	0/2	0/2	0/2	0/2	0/2	0/2
1 (cage contact)	...	0/1	0/1	0/1	0/1	0/1	0/1
1 (room contact)	...	0/1	0/1	0/1	0/1	0/1	0/1
4	$10^{4.5}$	1/4	1/4	0/4	4/4‡	0/4	4/4§
2	$10^{4.0}$	1/2	2/2	0/2	2/2	0/2	2/2
2	$10^{3.5}$	1/2	0/2	0/2	2/2	0/2	2/2
4	$10^{5.0}$	1/4	0/4	0/4	4/4	0/4	4/4

* Numerator = number responding; denominator = number tested.
† 5-6 weeks' postinoculation serums.
‡ Range of complement-fixing antibody, 1:64 to 1:1024.
§ Range of neutralizing antibody, 1:32 to 1:320.

Inoculation of Subjects

Monkeys.—Cynomolgus monkeys of either sex were strictly isolated for four weeks after their arrival from the Philippines. Their serums were tested for measles complement-fixing antibodies immediately on arrival and again four weeks later. Only monkeys free of measles antibodies were used for these studies.

Inoculation of Monkeys with Measles Vaccine by Oral and Intramuscular Routes.—Susceptible monkeys were inoculated orally with 1 ml. of measles vaccine by dripping the virus into the open mouth with a syringe and an attached dull needle. Additional susceptible monkeys were each injected intramuscularly with about the same amount of virus. For each route, control monkeys were inoculated with normal tissue culture fluid and kept in separate quarters. Two susceptible monkeys were added to each inoculated group 24 hours after the virus was administered. In each instance, one susceptible monkey was placed in the same cage with an infected one. The other was kept in a separate cage in the same room to serve as a room-contact control. All monkeys were observed daily for rash or other signs of illness and their rectal temperatures were taken. White blood cell count, specimens for virus isolation, and serum for serologic tests were taken at the same time for all monkeys.

Intercerebral Inoculation of Monkeys with Measles Vaccine.—A group of monkeys was inoculated with 0.5 ml. of measles vaccine intercerebrally. Control monkeys were each inoculated in the same manner with normal tissue culture fluid. No contact monkeys were used. All monkeys were carefully observed and studied histopathologically, but viremia studies were made in only a few.

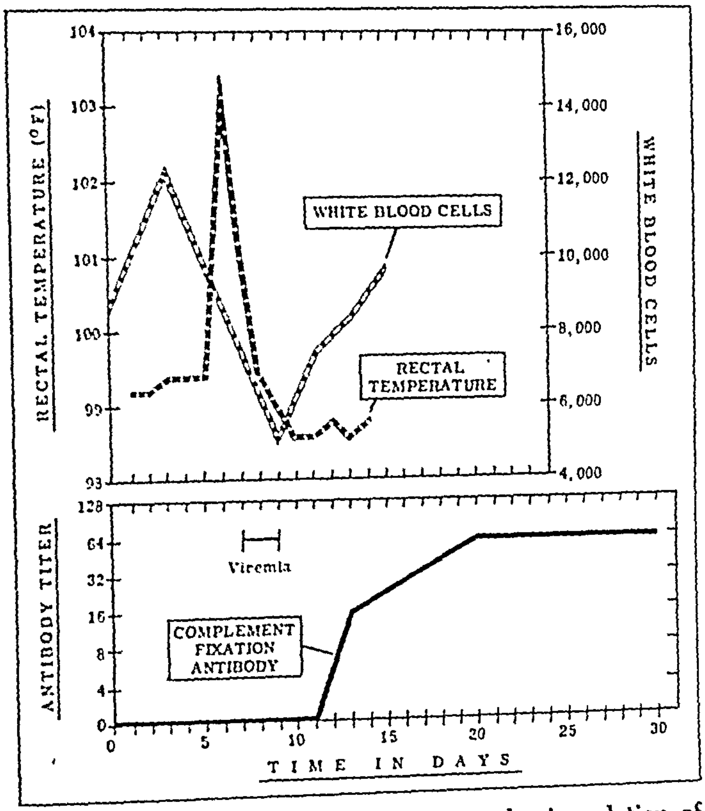

Fig. 1.—Data obtained after intramuscular inoculation of 2½-year-old child with $10^{3.5}$ $TCID_{50}$ of live, modified measles virus.

Inoculation of Monkeys with Distemper Vaccine.—Susceptible monkeys were inoculated intramuscularly and intercerebrally in the same manner and with the same amounts as with measles vaccine. Control monkeys were inoculated with normal tissue culture fluid; no contact control animals were used.

Reinoculation of Vaccinated Monkeys.—Monkeys previously vaccinated with distemper vaccine were reinoculated with measles vaccine, in some cases receiving 1.0 ml. intramuscularly, in others 0.5 ml. orally and 0.5 ml. intranasally. Monkeys previously inoculated with measles virus were revaccinated with 1 ml. of distemper virus intramuscularly, and some monkeys previously inoculated with distemper virus intramuscularly received a second similar injection.

Human Volunteers.—Blood samples from children in a guardian home who had no history of previous measles infection were tested for measles complement-fixing antibodies. Only 2 of 16 children had negative serums and could be used for this study.

Viremia and Throat Cultures.—Blood specimens for virus isolation and white blood cell count were taken from monkeys and from the human volunteers every 2nd day for 15 days, beginning with the 3rd day after inoculation. Two to five tubes were inoculated with 1.5 to 2.0 ml. of whole, heparinized blood, with use of human amnion tissue culture (HATC) and human heart tissue cells (HHTC). Throat cultures were taken at the same intervals by swabbing the pharynx with sterile cotton which was then submerged, and agitated vigorously, in 2 ml. of tissue culture fluid containing 2,000 units of penicillin, 2,000 mcg. of streptomycin, and 50 to 100 units of nystatin (Mycostatin) per milliliter. After 30 minutes at room temperature, the cotton was squeezed out and discarded. The fluid was inoculated in amounts of 0.2 ml. into each of three to five tubes. HATC was observed for about 30 days and HHTC for 14 days. One blind passage was performed. Isolations were identified by serum-neutralization tests. Attempts to isolate distemper virus from the blood or throat were made by inoculating 0.1 ml. of fluid into the chorioallantoic membrane of each of several embryonated eggs.

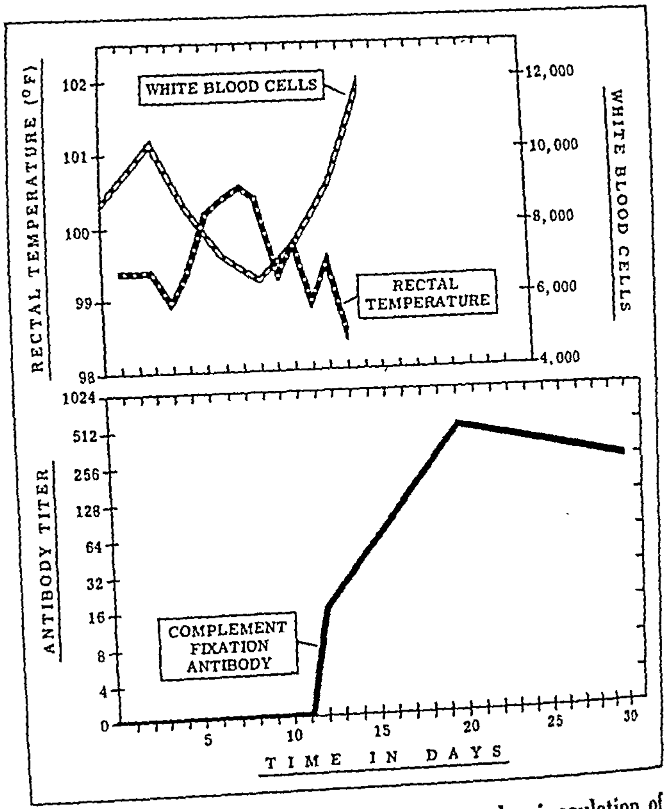

Fig. 2.—Data obtained after intramuscular inoculation of 4-year-old child with $10^{3.5}$ $TCID_{50}$ of live, modified measles virus.

Results

Modified Live Measles Vaccine.—Results of studies with modified live measles vaccine administered by different routes to monkeys and human volunteers were as follows.

Inoculation of Monkeys by Oral and Intramuscular Routes: As can be seen in tables 1 and 2, virus could be found in the blood of two of four, and in the throats of three of four, orally inoculated monkeys. Among the intramuscularly inoculated monkeys, viremia could be demonstrated in only 4 of 12, while virus could be isolated from the throats of 3 of 13. These virus isolations were demonstrated in human heart cells only, not in human amnion cells. In no instance could measles virus be isolated from the control or contact monkeys. Furthermore, the absence of measles antibodies in the serums of contact monkeys clearly indicated that they were not infected by contact with virus-inoculated monkeys. Neither infected, control, nor contact monkeys showed any signs of illness, rash, fever, or significant leukopenia. However, all monkeys inoculated with virus, regardless of the route of inoculation, developed complement-fixing and neutralizing measles antibodies.

TABLE 3.—*Results of Intramuscular and Intercerebral Inoculation of Distemper Vaccine into Cynomolgus Monkeys*

			Preinoculation and Postinoculation Antibody Response*					
			Measles					
			Complement-fixing		Neutralizing		Distemper Neutralizing	
No. of Monkeys	Route	Amount, EID_{50}	Before	After	Before	After	Before	After
4	I.M.	$10^{5.5}$	0/4	1/4†	0/4	0/4	0/4	4/4‡
4	I.M.	$10^{5.2}$	0/4	1/4§	0/4	0/4	0/4	3/3
2	I.C.	Normal tissue culture fluid	0/4	0/4	0/4	0/4	0/4	0/4
1	I.C.	$10^{4.9}$	0/1	0/1	0/1	0/1	0/1	Not tested
4	I.C.	$10^{5.2}$	0/4	0/4	0/4	0/4	0/4	3/4¶

* Numerator=number responding; denominator=number tested.
† Complement=fixation titer 1:16.
‡ Distemper neutralizing antibody range; 1:10 to>1:1000.
§ Complement-fixation titer 1:4.
¶ One serum not tested.

Intercerebral Inoculation of Monkeys: Viremia studies were performed on only 4 of 12 monkeys inoculated intercerebrally with measles vaccine. Virus could be isolated from the blood of one on the fifth day and from that of another on the seventh day. No attempts were made to isolate virus from the throat or spinal fluid. No damage due to measles virus could be detected, however, either clinically or histopathologically. All monkeys inoculated with virus developed measles antibodies, while the control animals remained susceptible.

Inoculation of Human Volunteers: Two children, aged 2½ and 4 years, were inoculated intramuscularly with 1 ml. of measles vaccine containing $10^{3.5}$ $TCID_{50}$ of virus. Figures 1 and 2 demonstrate the results of this experiment. In both children, a fever was noticed six to seven days after inoculation which lasted from two to four days. A decrease in the white blood cell count was also observed. No rash or Koplik spots and only a mild tonsillitis was found on physical examination. Virus could not be isolated from the throat of either child but was demonstrated in the blood of one child on the seventh and the ninth day. Both children developed complement-fixing and neutralizing measles antibodies.

Distemper Vaccine.—Results of studies with distemper vaccine administered to monkeys by different routes were as follows.

None of the intramuscularly or intercerebrally inoculated monkeys showed any clinical signs such as fever, rash, or paralysis. Virus isolations were attempted from the blood and throats of four intramuscularly inoculated monkeys, but no virus could be recovered. Table 3 demonstrates that all virus-inoculated monkeys, with the exception of one inoculated intercerebrally, developed significant distemper-neutralizing antibodies. However, measles-neutralizing antibody could not be demonstrated in any of these monkeys, although 2 of 13 did show some low measles complement-fixing antibody.

TABLE 4.—*Results of Inoculation of Live Measles Vaccine into Cynomolgus Monkeys Previously Inoculated with Distemper Vaccine*

			Neutralizing Antibody Titer							
					Postinoculation Wk.					
	Inoculation		Day of Inoculation		1		2		3	
Monkey, No.	Route*	Amount $TCID_{50}$†	Measles	Distemper	Measles	Distemper	Measles	Distemper	Measles	Distemper
251................	I.M.	$10^{5.2}$	0	1:500	0	1:10,000	1:32	1:100,000	1:320	1:100,000
255................	I.M.	$10^{5.2}$	0	1:1,000	0	1:400,000	1:10	10^6	1:32	$1:10^6$
253................	I.N. & oral	$10^{5.2}$	0	1:320	0	1:50	1:32	1:10,000	1:32	1:10,000
254................	I.N. & oral	$10^{5.2}$	0	1:320	0	1:100	1:32	1:10,000	1:320	1:10,000
73................	I.M.	$10^{3.2}$	0	1:200	0	$1:10^6$	1:32	$1:10^6$	1:320	$1:10^6$
229†................	I.M.	$10^{3.2}$	0	N.T.	0	N.T.	1:2	N.T.	1:20	N.T.

* I.M. = intramuscular; I.N. = intranasal.
† N.T. = Not tested.

Six monkeys which responded to distemper virus inoculation with good distemper antibody development were reinoculated with 1.0 ml. each of live measles virus: four intramuscularly and two each with 0.5 ml. intranasally and 0.5 ml. orally. In table 4 it will be seen that neither an accelerated nor a higher measles antibody response occurred in these monkeys. Measles antibodies developed two weeks after inoculation and reached a level expected after a primary inoculation in nonsensitized monkeys. A typical "booster" effect occurred, however, for the distemper antibodies in the intramuscularly inoculated monkeys, but two weeks elapsed before an increase in titer was noted for the orally inoculated animals.

In another experiment, three monkeys with good measles complement-fixing and neutralizing antibodies, as well as distemper antibodies due to a measles virus inoculation, were injected intramuscularly with distemper virus. This resulted in a marked increase in distemper antibody, but in only one monkey was there a significant increase in measles-neutralizing antibodies. No significant rise in measles complement-fixing antibodies could be demonstrated (table 5). Even when two additional monkeys were inoculated intramuscularly a second time with distemper vaccine, no measles-neutralizing antibody could be found in their blood. A low-level measles complement-fixing antibody titer in one monkey, found after the first injection, did not increase after the second. In the second monkey, measles complement-fixing antibodies did not develop at all. In contrast, the distemper antibody level increased significantly in both monkeys (table 6).

TABLE 5.—*Results of Intramuscular Inoculation of Distemper Vaccine* in Cynomolgus Monkeys Previously Inoculated with Live Measles Vaccine*

	Antibody Titers											
	Day of Inoculation			Postinoculation wk. 1			2			3		
	Measles			Measles			Measles			Measles		
Monkey, No.	Complement-fixing	Neutralizing	Distemper	Complement-fixing	Neutralizing	Distemper	Complement-fixing	Neutralizing	Distemper	Complement-fixing	Neutralizing	Distemper
217............	1:512	1:32	1:10	1:256	1:320	1:500	1:256	1:320	1:32,000	1:128‡	1:320‡	1:32,000
218............	1:256	1:320	1:100	1:512	1:320	1:500	1:512	1:320	1:1,600	1:256	1:320	1:10,000
237............	1:1,024†	1:200	1:50	1:512	1:320	1:50	1:512	1:320	1:500	1:256	1:320	1:1,000

* $10^{5.5}$ egg-infective dose (EID_{50}) of virus inoculated per monkey.
† Titer of serum 7 days prior to inoculation.
‡ Titers of 4 wk. postinoculation serums.

TABLE 6.—*Results of Intramuscular Inoculation of Distemper Vaccine* in Cynomolgus Monkeys Previously Immunized with Distemper Vaccine*

	Antibody Titers											
	Day of Inoculation			Postinoculation wk. 1			2			3		
	Measles			Measles			Measles			Measles		
Monkey, No.	Complement-fixing	Neutralizing	Distemper	Complement-fixing	Neutralizing	Distemper	Complement-fixing	Neutralizing	Distemper	Complement-fixing	Neutralizing	Distemper
113............	1:8	0	1:1,600	1:8	0	$1:10^6$	1:16	0	$1:10^6$	1:16	0	$1:10^6$
235............	AC†	NT‡	1:32	NT	0	1:63,000	0	0	1:32,000	0	0	1:2,000

* $10^{5.2}$ egg-infective dose 50% (EID_{50}) of virus inoculated per monkey.
† Anticomplementary.
‡ Not tested.

Comment

The live measles vaccine tested in these experiments did not cause any signs of illness when inoculated orally, intramuscularly, or intercerebrally in susceptible monkeys but resulted in good antibody production. The same vaccine, when injected into two children, caused a good immunologic response but also a mild illness with fever, sore throat, and a decreased white blood cell count. It seems, therefore, that man is much more sensitive to measles virus infection than is the monkey. This leads to the conclusion that, at present, only man himself can be used as a definite indicator of virulence of a measles vaccine. Our findings, in monkeys as well as in man, seem to confirm the results obtained by Enders and co-workers[4] and Katz and Enders.[5] However, Enders' group was unable to isolate the virus from the blood of either monkeys or human subjects inoculated with the attenuated virus while, in several instances, we were able to do so. Different isolation techniques may have caused this variation in results, for it is not surprising that a viremia could occur after inoculation with a modified live virus which is still capable of producing a mild generalized illness. In our experiments, we attempted the virus isolations in both human heart tissue cells (HHTC) and in human amnion tissue culture (HATC). In all instances, virus was isolated in human heart cells only, while we could not demonstrate it in the HATC inoculated with the same material. This suggests that HHTC is a better indicator for small amounts of virus. The measles cytopathogenic effect appears earlier in HHTC than in amnion cells, hence the former cultures can be observed for a shorter time, thus eliminating many problems which arise when cultures must be kept for a long period. Further, HHTC, as a continuous cell line, is probably more uniformly sensitive to the virus, while primary tissue cultures, such as human amnion, may vary in their virus susceptibility from batch to batch.

The fact that susceptible monkeys in direct contact with inoculated ones did not become infected, even though virus could be recovered from the throats of some vaccinated monkeys, indicated that infectiousness of the modified virus by the natural route was significantly decreased. This lack of spread with modified virus was also demonstrated by Katz and Enders [5] in studies with children.

The work with distemper virus showed that no disease occurred when susceptible monkeys were inoculated and that significant distemper antibody levels appeared. No demonstrable measles-neutralizing antibodies developed, however, even after two injections of live distemper vaccine, and measles complement-fixing antibodies were either absent, or present at a low level. Inoculation of monkeys possessing distemper, but not measles, antibodies with measles vaccine did not result in an accelerated, or higher, measles antibody response. Neither, with one exception, did an injection of distemper virus in monkeys possessing measles antibody result in a significant increase in measles antibodies.

One can conclude from these findings that, even though measles and distemper viruses may share some genetic characteristics, the particular strain of distemper virus used lacks, to a high degree, the antigenic component which would cause significant measles antibody production. On the other hand, the measles virus tested exhibited a more complete antigenic composition, leading to the development of both measles and distemper antibody. It would appear, therefore, that vaccination with this strain of distemper virus is of limited value as a means of protection against measles. The second paper published in this issue provides further evidence on this point.

Summary

The inoculation of a modified live measles vaccine into monkeys by different routes resulted in good antibody development, with no signs of illness; however, virus could be isolated from the blood and throats of some monkeys. The same vaccine inoculated into two human volunteers produced not only a good antibody response but also a mild illness, and virus was isolated from the blood of one child. Inoculation of monkeys with distemper virus did not produce significant measles antibody levels. The value of distemper vaccination in producing antibodies to combat measles appears questionable, therefore, when judged on the basis of these experiments with monkeys.

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Dr. J. F. Enders, Children's Medical Center, Boston, supplied the Edmonston strain of measles virus used in this study, and Dr. J. W. Newberne, Pathology Department, Pitman-Moore Company, made the histopathological studies on monkeys.

The human heart tissue cells used in this study were supplied by Microbiological Associates, Washington 14, D. C.

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EXPERIMENTAL VACCINATION AGAINST MEASLES

II. TESTS OF LIVE MEASLES AND LIVE DISTEMPER VACCINE IN HUMAN VOLUNTEERS DURING A MEASLES EPIDEMIC IN PANAMA

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During a measles epidemic in Panama, 453 persons with no previous history of measles were inoculated with a modified live-virus measles vaccine, and 356 others served as controls. About 70 to 80% of children under 5 years of age had some degree of fever, and about 50% of these developed a slight macular rash. During the following four and one-half months, three of the vaccinated group developed measles, compared with 32 among the controls. In addition, 388 persons were vaccinated with canine distemper vaccine, with 414 controls. None showed reactions to the vaccine. In the following three to four months, 14 cases of measles occurred in the vaccinated group and 25 among the controls. It is concluded that the measles vaccine was effective but caused some reaction, while the ability of this strain of distemper virus to protect against measles appears to be low.

Experiments with a modified live measles vaccine in monkeys and in two children described in the foregoing paper in this issue showed that the vaccine caused no noticeable disease in monkeys, although a mild illness was observed in the children. Vaccination was, however, followed by development of a good measles antibody response in both monkeys and children. It appeared, therefore, that a more extensive trial of this vaccine in human subjects would be justified, especially in a region where a large, susceptible population might be threatened by a measles epidemic. Such a situation occurred in Panama in the spring of 1959. This paper describes tests of the measles vaccine in a large population group during this epidemic in Panama. The possible value of vaccination with canine distemper virus as a prophylaxis against measles was also investigated at the same time.

Materials and Methods

Measles and Distemper Vaccine.—The preparation and the safety and potency tests of these tissue culture vaccines have been described in the previous paper in this issue. Lyophilized vaccine was shipped under refrigeration by air express. The measles vaccine contained $10^{3.0}$ tissue culture infective doses 50% ($TCID_{50}$) per 0.2 ml. of virus when titered in human heart tissue culture prior to shipment. The *distemper vaccine, titered in embryo*nated hens' eggs, contained $10^{4.2}$ egg infective doses 50% (EID_{50}) per 0.1 *ml.*

Serologic Tests.—A small number of serum samples were taken for serologic *studies from persons* having clinical measles as well as from vaccinated groups. All serums were kept frozen and sent to the Virus Research Laboratories, Pitman-Moore Company, Indianapolis, where they were tested for measles complement-fixing and neutralizing antibodies, as well as for distemper-neutralizing antibodies by methods described in the previous paper *in this issue.*

Epidemiologic Background.—Field evaluation of the vaccines was conducted at the Chiriqui Land Company (United Fruit Company) banana plantations on the Pacific side of western Panama near the Costa Rican border. The general area consists of the port town of Puerto Armuelles with about 10,000 population, and 28,000 acres of banana farn with about 12,000 population. A distance of 10 mil separates the port town from the closest banar farms. About each 1,000 acres of farm land has labor camp consisting of houses and barracks. Th average temperature is in the high 80's, with hig humidity, and rainfall averages 90 in. per year.

Measles is endemic in this region and becom epidemic every few years. At such times it is likel to severely affect the laborers and their familie who come in from other areas, especially Indian such as the Guaymi. It is difficult to estimate th precise incidence of infectious diseases such a measles for two reasons: (1) many infections ar treated by trained dispensators living on the farms and, although treatment is adequate, complete accuracy of diagnosis cannot always be depended on: and (2) many persons with mild or moderate infections remain in quarters and do not come to the attention of any medical person. All patients with severe cases are sent to the 200-bed hospital of the Chiriqui Land Company at Puerto Armuelles. Thus, records of hospitalized patients can be used to arrive at a rough index of incidence, if it is realized that for every hospitalized patient there may be two to five not hospitalized.

From the Chiriqui Land Company (United Fruit Company) (Drs. Hoekenga and Palma), and the Research Division, Pitman-Moore Company (Drs. Schwarz and Boyer).

Table 1 shows the number of persons hospitalized for measles during the first eight months of 1959, according to age groups. It will be seen that the incidence of measles in or near Puerto Armuelles did not vary greatly during this period. On the other hand, measles infections originating on the farms increased abruptly in March, continued high for about three and one-half months, and then fell off. By the end of August, the incidence was down to a preepidemic level. This pattern was probably due to the fact that a large number of Indians and their families came from relatively isolated areas to work on the farms and therefore represented a more susceptible population. While most cases occurred in small children, older children and young adults also were involved. About one-half of the patients were mestizos (mixed racial strains) and the other half Indians. Sixty-five per cent were male and 35% female. The total number of personnel hospitalized for measles, 256, represents 2% of the farm population. It is possible that another 6 to 10% of this population had measles during the epidemic but did not undergo hospitalization. The severity of the outbreak is indicated by the fact that nine of the hospitalized children died from overwhelming disease with bronchopneumonia, in spite of supportive and antibiotic treatment.

TABLE 1.—*Age Distribution of Patients and Geographic Location* of Hospitalized Measles Cases, January-August, 1959*

Age Group, Yr.	Month																Total	
	Jan.		Feb.		March		April		May		June		July		Aug.			
	Port*	Farms*	Port	Farms	Port	Farms	Port	Farms	Port	Farms	Port	Farms	Port	Farms	Port	Farms	Port	Farms
Under 2	5	2	5	9	7	11	7	16	3	12	0	9	1	7	2	2	30	68
2- 5	2	1	4	1	0	23	2	16	1	19	6	5	1	1	1	2	17	68
6-10	0	1	0	2	2	5	0	2	0	10	0	4	0	1	0	0	2	25
11-15	0	0	0	3	0	4	1	2	1	2	1	3	0	0	1	0	4	14
16-20	0	1	0	2	0	10	0	9	0	10	1	12	0	2	0	2	1	48
21-25	0	0	0	1	0	7	0	5	0	7	0	5	0	3	1	0	1	28
26-30	0	0	0	0	0	1	0	0	0	4	0	0	0	0	0	0	0	5
Total	7	5	9	18	9	61	10	50	5	64	8	38	2	14	5	6	55	256
	12		27		70		60		69		46		16		11		311	

*"Port" refers to town of Puerto Armuelles, "Farms" refers to labor camps in nearby banana farms.

TABLE 2.—*Measles and Distemper Antibody in Serum Specimens Taken in Acute and Convalescent Stage of Disease*

Age of Patients, Yr.	Antibody Titers					
	Measles, Complement Fixing		Measles, Neutralizing		Canine Distemper Neutralizing	
	Acute Phase	Convalescent Phase	Acute Phase	Convalescent Phase	Acute Phase	Convalescent Phase
1	0	1:625	0	1:32	1:32	1:5,000
1½	0	1:1,024	1:6	1:320	1:32	1:320
2	1:256	1:128	1:200	1:320	1:250	1:630
2	1:2	1:128	1:10	1:32	1:500	1:2,000
3	1:64	1:512	0	1:320	1:100	>1:1,000
3	1:8	1:125	1:6	1:32	1:20	1:32
4	0	1:625	1:4	1:320	1:630	1:1,000
18	0	1:125	0	1:32	0	1:1,600
18	0	1:125	0	1:320	1:1,000	1:5,000
20	0	1:125	1:20	1:200	1:10	1:320
20	1:25	1:125	1:6	1:20	1:10,000	1:25,000
20	1:2	1:3,125	0	1:320	1:5,000	>1:100,000
22	0	1:625	1:3	1:32	0	1:160
22	1:125	1:125	1:32	1:320	1:3,200	>1:100,000
23	1:10	1:10	1:32	1:20	1:160	1:320

To confirm serologically that this outbreak was measles, serum samples were taken from 15 patients during the first few days of illness and samples in the convalescent phase from the same persons three weeks later. Eleven of 15 paired serum samples from the acute and convalescent phases showed a significant increase in measles complement-fixing, or neutralizing antibodies, or both. The same serum samples were also tested for distemper-neutralizing antibodies, and a definite antibody rise could be noted in most serums of the convalescent phase (table 2).

Vaccination Procedure.—In mid-March, 1959, farms which had had the greatest number of measles patients hospitalized during the previous two months were chosen for vaccination. The farm living centers were surveyed, house by house, with particular attention to persons under 30 years of age who had not had measles. This could, for practical reasons, be determined only on the basis of a clinical history. Of 4,263 persons surveyed, 1,611 under 30 years of age had no history of clinical measles. The vaccine was offered to this group. All who accepted were inoculated, while the remainder served as controls. This selection did not, in our opinion, influence the design of the experimental study, since all groups tested were from the same socioeconomic level. Labor camps not involved in the measles virus vaccination program were used for the distemper study. Table 3 lists the number of persons vaccinated with either measles or distemper vaccine, together with the corresponding control groups.

TABLE 3.—*Populations Involved in Measles Vaccination Program, Puerto Armuelles, Panama, 1959*

Vaccine	Total Population	No. of Persons Under 30 Years Who Had Not Had Measles	No. of Persons Vaccinated	No. of Unvaccinated Controls
Measles	2,156	809	453	356
Distemper	2,107	802	388	414
Total	4,263	1,611	841	770

The vaccines were kept refrigerated, and each vial was restored to its original volume with sterile distilled water just before use. Children under 5 years of age were inoculated intramuscularly with

0.5 ml. of the indicated vaccine, while all other persons received 1.0 ml. by the same route. The injections were made by a physician or qualified public health nurse under the physician's direction. After vaccination, house-to-house checks for reactions were made by trained personnel. All patients reporting to the dispensaries were also examined for possible measles and, in many cases, a physician confirmed the diagnosis. Later, measles incidence was determined by a systematic survey of the farms every two weeks and by monthly reports from the dispensaries.

Results

Clinical Reactions to the Vaccines.—No reaction or signs of illness were found in volunteers inoculated with distemper vaccine, either on the day of inoculation or later. With measles vaccine, no immediate reactions were observed. However, about 70 to 80% of the children under 5 years of age had some degree of fever, usually about the 6th to 8th day after vaccination, although occasionally as late as the 9th or 10th day. The fever usually was mild, but in some instances the rectal temperature reached 105 F (40.6 C). About 50% of the children developed a slight pink macular rash lasting from one to four days. This rash usually was limited to a few spots but was generalized in about 5%. Koplik's sign was found in at least four instances. Nine children were hospitalized for reactions, but it was believed that only four really needed hospital care; the other five arrived at the hospital at night and were retained because of the limited transportation facilities. The average hospitalization of these children was five days, the time varying from 2 to 10 days. There appeared to be a correlation between the severity of the reaction and the nutritional state of a child, the most marked reactions occurring in poorly nourished infants. Children 5 years of age or older, and adults inoculated with measles vaccine, did not have any signs of illness, though mild fever may have occurred without being noticed.

TABLE 4.—*Measles and Distemper Antibody Response in Volunteers Inoculated with Measles Vaccine*

Age of Volunteers, Yr.	Prevaccination and Postvaccination Antibody Titer					
	Measles Complement-fixing		Measles Neutralizing		Distemper Neutralizing	
	Before	After	Before	After	Before	After
3	0	1:100	0	1:32	0	1:1,000
4	0	1:625	0	1:32	0	1:32
5	AC*	1:100	0	1:32	0	1:160
6	0	1:5	1:32	1:32	1:10,000	1:50,000
8	0	1:625	0	1:100	0	1:1,000
9	1:2	1:2	1:20	1:20	1:5,000	1:320
11	1:4	1:100	1:32	1:20	1:6,300	1:1,600
13	AC*	1:4	1:4	1:32	0	1:100
20	0	0	1:32	1:32	1:10,000	1:100,000
20	1:125	1:125	1:200	1:320	1:4,000	1:5,000
22	1:5	1:5	1:64	1:320	1:320	1:2,000
22	0	1:625	0	>1:320	1:10	1:1,000
29	1:25	1:25	>1:32	>1:32	1:1,000	1:630

* AC=anticomplementary.

Antibody Response in Vaccinated Groups.—Results obtained when the small number of preinoculation and postinoculation serum specimens from volunteers inoculated with measles vaccine were tested for measles complement-fixing, measles neutralizing, and distemper-neutralizing antibodies are shown in table 4. All persons, with one exception, who lacked measles antibody on the day of vaccination developed significant antibody three weeks after inoculation. Furthermore, volunteers inoculated with the measles vaccine, and who lacked distemper antibody on the day of vaccination, developed significant levels of neutralizing distemper antibodies.

TABLE 5.—*Distemper and Measles Antibody Response in Volunteers Inoculated with Distemper Vaccine*

Age of Volunteers, Yr.	Prevaccination and Postvaccination Antibody Titer					
	Distemper Neutralizing		Measles Complement-fixing		Measles Neutralizing	
	Before	After	Before	After	Before	After
7	1:16	1:1,000	0	1:5	0	>1:32
7	0	1:50	AC*	1:2	0	1:2
8	1:3,200	1:3,200	1:32	1:16	1:320	1:64
8	1:3,200	1:50,000	1:128	1:128	>1:320	1:320
8	1:100	1:10,000	1:625	1:125	1:320	1:320
8	1:10,000	1:100,000	1:125	1:125	1:320	1:320
9	0	1:63	0	1:5	0	1:4
10	1:1,000	1:5,000	1:25	1:25	1:200	1:320
11	1:10,000	1:100,000	1:125	1:125	1:320	1:320
12	1:500	1:10,000	1:64	1:64	>1:320	>1:320
14	1:1,000	1:3,200	1:4	1:4	>1:32	>1:32
14	1:320	1:5,000	1:4	1:5	1:320	1:320
16	1:20,000	1:32,000	1:25	1:125	>1:32	>1:320
19	1:320	1:5,000	1:32	1:32	1:320	1:100
20	1:10,000	1:10,000	AC*	1:5	1:32	1:32

* AC = anticomplementary.

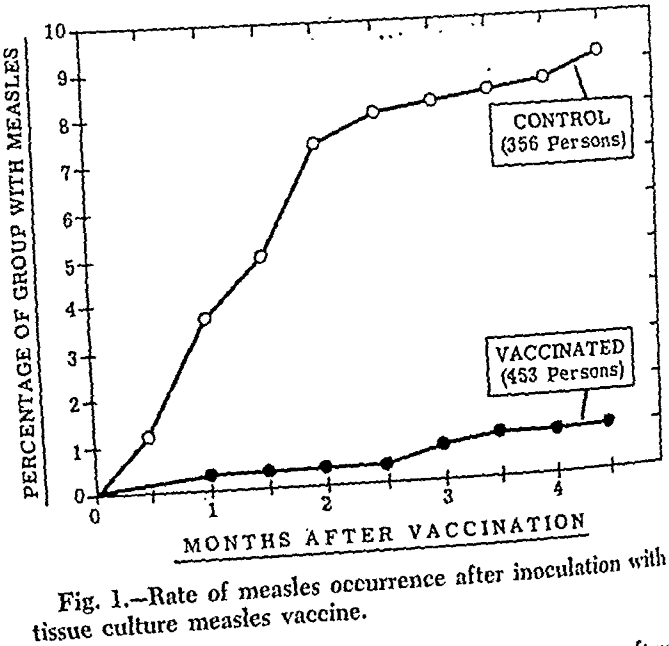

Fig. 1.—Rate of measles occurrence after inoculation with tissue culture measles vaccine.

The immunologic response of volunteers after distemper vaccine inoculation is summarized in table 5. While only two subjects had serums negative for distemper antibody before receiving distemper vaccine, both developed distemper antibody as well as low-level measles antibody three weeks after vaccination.

In 10 children having distemper antibodies prior to vaccination with distemper vaccine, a significant increase in the distemper antibody titer occurred, but without similar increases in measles antibody.

Incidence of Measles in Vaccinated Volunteers.—Table 6 and figure 1 detail the occurrence of measles in the vaccinated and control groups during the four and one-half months after use of the measles vaccine. Only 0.7% of the vaccinated subjects developed disease, although measles occurred in 9.0% of the nonvaccinated control group, which represents a thirteenfold difference. The beneficial effect of this vaccine is even more remarkable when one considers the statistics for children 5 years of age and younger—the ages at which serious illness and death occurred during this epidemic. Among 243 vaccinated children of this age group, there were two cases of measles, or an incidence of 0.8%. There were 16 cases among 103 controls, or an incidence of 15.5%. Figure 1 shows the occurrence of measles in terms of time after inoculation and demonstrates graphically the efficacy of this vaccine.

TABLE 6.—*Occurrence of Measles in Four-and-One-Half-Month Period After Inoculation with Tissue Culture Measles Vaccine*

	Vaccinated			Controls		
		Measles Cases			Measles Cases	
Age Group, Yr.	No. of Persons	No.	%	No. of Persons	No.	%
Under 2	108	2	0.8	53	6	15.5
2- 5	135	0		50	10	
6-10	85	0	0.0	39	4	5.7
11-15	32	0		31	0	
16-20	37	0	1.1	68	6	6.6
21-25	35	1		67	4	
26-30	21	0		48	2	
	453	3	0.7	356	32	9.0

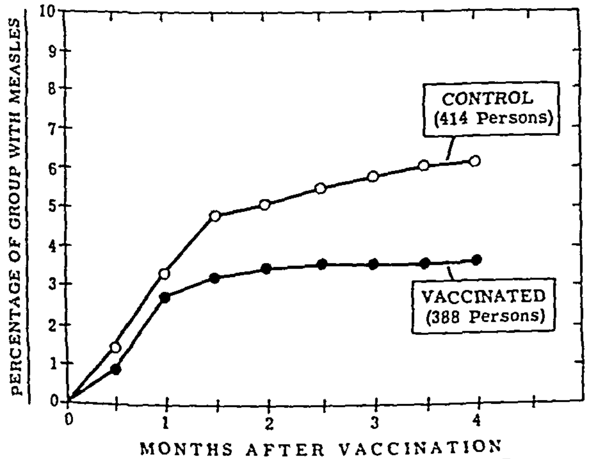

Fig. 2.—Rate of measles occurrence after inoculation with tissue culture distemper vaccine.

The degree of protection against measles after the use of distemper vaccine is summarized in table 7, as well as in figure 2. The over-all incidence of measles in the vaccinees was 3.6% compared to 6.0% in the control groups. As may be noted in table 7, however, if only children up to 5 years of age are considered, the value of the distemper vaccine appears more favorable. Among 221 vaccinated children of that age group, there were 9 cases of measles, or an incidence of 4.1%, while among the 116 controls there were 14 cases, or an incidence of 12.1%. This difference appears to be statistically significant.

Comment

In considering the relative merits of the measles and distemper vaccines used in this study, attention must be given to their efficacy in the prevention or modification of measles, on the one hand, and to vaccine reactions on the other. In our vaccination program, for instance, we were interested primarily in the reduction of infant morbidity and mortality, but we were also interested in eliminating measles as a cause of absenteeism among young laborers. In other locations or circumstances, this second goal may not be important.

In the over-all picture, it is apparent that the measles vaccine provided good protection in all age groups. It must be emphasized, though, that vaccine reactions were somewhat severe in some children, even to the point of requiring hospitalization of a few. Since hospital facilities were available to these people at no cost, and since even a marked vaccinal reaction was preferable to the risk of the naturally occurring disease in infants, it was thought that the reactions would neither constitute a drawback for use in the Panama area nor prevent the use of the measles vaccine in many other areas. It is possible, however, that in some parts of the world the rather high reaction rate might be considered a contraindication to the use of this vaccine in small children. Further attenuation of the virus should eliminate this problem.

TABLE 7.—*Occurrence of Measles in Three-to-Four-Month Period after Inoculation with Tissue Culture—Distemper Vaccine*

	Vaccinated			Control		
		Measles Cases			Measles Cases	
Age Group, Yr.	No. of Persons	No.	%	No. of Persons	No.	%
Under 2	80	5	4.1	53	5	12.1
2- 5	141	4		63	9	
6-10	80	3	3.1	58	3	4.0
11-15	18	0		41	1	
16-20	30	1	3.0	61	3	3.5
21-25	21	0		73	3	
26-30	18	1		65	1	
	388	14	3.6	414	25	6.0

The results with use of the distemper vaccine do not demonstrate much value, especially in older children and young adults. However, the threefold difference in young children—4.1% among vaccinees and 12.1% among controls—is worth noting. Even though significant protection was found in this age group, it is thought that the potency of this particular distemper virus for protection against measles is too low to be generally useful. It appears at present, on the basis of the facts in the previous paper in this issue as well as in this report, that measles and distemper viruses are related antigenically but not to the extent where a distemper virus inoculation would give satisfactory protection against measles. Serologic studies in monkeys, as well as in these human volunteers, indicate that inoculation with measles virus results in the production of distemper antibody as well as measles antibody, while the distemper strain used gives rise to marked distemper antibodies but to only very low, or negative, measles antibody response. Further studies along these lines, with use of different distemper virus strains, might give more favorable results.

Summary

In 1959, a moderate measles epidemic occurred in the banana plantations of western Panama. During this epidemic, 453 persons were inoculated with a tissue culture measles vaccine, 356 others serving as controls. In addition, 388 persons were vaccinated with a tissue culture distemper vaccine, 414 others serving as controls.

It was concluded that, while the measles vaccine was effective, the high rate of reactions limits its usefulness. On the other hand, no reactions could be found due to the distemper vaccine, but the ability of this vaccine to protect against measles appeared to be limited.

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EXCRETION OF RADIOIODINE IN HUMAN MILK

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The possibility that I^{131} administered to a lactating woman might appear in the milk and might reach the nurseling in harmful amounts was studied in six nursing mothers. Most of them were already in the process of weaning their babies. The I^{131} was given by mouth to the mother in doses of either 10 or 30 µc just after the final breast feeding. The quantity of I^{131} that appeared in the milk secreted in 48 hours after administration was 1.4, 3.9, 0.14, 0.03, 6.2, and 26.8% of the total that had been administered, respectively, to the six mothers. Most of the I^{131} was secreted during the first 24 hours. It is recommended that candidates for diagnostic tests with I^{131} be questioned about lactation and that nursing should be interrupted for 24 hours, or, in the case of a large diagnostic or therapeutic dose, until measurements indicate that the I^{131} content of the milk is no longer significant.

It has been shown by several investigators that radioiodine (I^{131}) administered to lactating women will appear in the milk.[1] Since at times the amount of I^{131} appearing in the milk will be a hazard to the nursing infant, the lactating patient should always discontinue nursing during the course of the test. It should be a routine procedure to question female patients about lactation at the time I^{131} is administered. This precaution is not taken in some isotope laboratories, so it seems advisable to reemphasize that such a hazard exists.

We have been interested in determining how soon the patient might resume nursing after the administration of I^{131} and in correlating the milk excretion of I^{131} with plasma, urine, and thyroid content. We therefore obtained the cooperation of several nursing women who were willing to discontinue nursing for the period of the test.

Method

Studies were made of six nursing mothers. For the most part these women were already in the process of weaning their babies, but one patient (case 1) was feeding her baby only breast milk at the time the test was started. For this reason she had a considerably larger milk production during the course of the test.

Just before administration of I^{131} there was a final infant nursing. Thereafter every time the breasts became full they were manually stripped, and the total output was brought to the isotope laboratory. This was carried out for one week by patient 1 and for 48 hours by the others, with the exception of patient 6, by whom milk collections were discontinued after 24 hours.

Ten microcuries of I^{131} was administered by mouth to all patients with the exception of patient 1, who received 30 µc. Our routine dose for a simple 24-hour iodine uptake test is 5 µc or less. More was given to this group to insure adequate radioactivity for accurate measurement in the milk, plasma, and urine specimens.

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At intervals of 2, 6, 24, and 48 hours after I^{131} administration, measurement for radioactivity was also made (1) over the thyroid gland, (2) on a blood sample (for plasma level of radioactivity), (3) on all urine voided in each interval. In vivo measurements were made with the scintillation counter. In vitro measurements were made in a well scintillation counter.

TABLE 1.—*Percentage of Ingested I^{131} Present in Each Milk Collection*

Patient, No.	1		2		3		4		5		6	
	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose	Cc. Milk	% of Administered Dose
					1st 24 hours							
	120	5.5	79	0.24	20	0.35	...	...	...	...	58	0.19
	70	4.7	...	...	...	...	...	...	...	...	...	...
	152	7.1	61	0.63	22	0.75	8.0	0.11	10	0.03	94	1.55
	82	2.4	40	0.37	29	1.0	...	...	...	...	95	1.96
	218	3.6	...	...	39	0.7	...	...	...	...	98	1.83
					2nd 24 hours							
	183	1.9	...	...	38	0.50	...	...	...	...	50	0.68
	...	...	27	0.14	...	...	4.3	0.03	7.8	0.003	...	...
	135	0.87	...	...	32	0.46	...	...	...	...	...	...
	106	0.37	13	0.04	...	...	...	...	...	...	...	...
	200	0.37	...	...	58	0.20	...	...	...	...	...	...
Total........	1,266	26.81	220	1.42	238	3.96	12.3	0.14	17.8	0.033	395	6.2

Results

Quantity of Milk Produced.—There was enormous variation, as would be expected (table 1), in the quantity of milk produced. The smallest milk production for the 48-hour period was only 12.3 cc. and the largest was 1,266 cc.

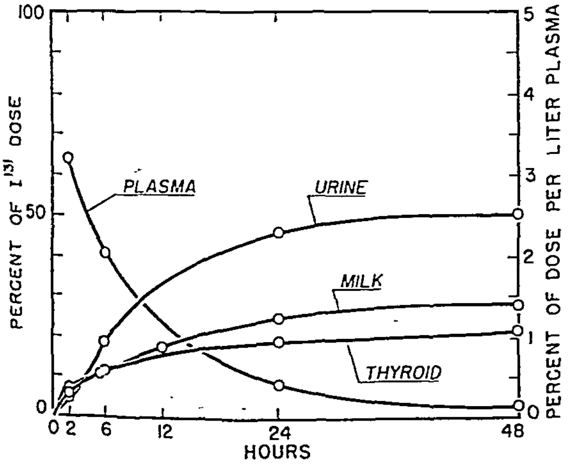

Fig. 1 (patient 1).—Curves of thyroidal uptake and cumulative milk and urine excretion expressed as percentage of ingested I^{131}. Plasma curve is expressed as percentage of ingested I^{131} per liter of plasma. Plasma and thyroid curves indicate low normal range of thyroid function. Forty-eight-hour total milk excretion of I^{131} is 26.8% of administered dose.

I^{131} Content of Milk.—The I^{131} content of the milk was roughly in proportion to the quantity of milk produced, as was previously demonstrated in I^{131} studies in cows.[2] In 48 hours the patient with the largest milk production excreted 26.8% of the administered dose of I^{131} in her milk. Figure 1 shows the cumulative curve of the milk excretion of I^{131} expressed in percentage of administered dose. It may be seen from this that most of this (23.3%) was excreted during the first 24 hours, so that there was a relatively small additional amount of I^{131} excreted in the milk during the second 24-hour period.

Plotted on semilog paper (fig. 2) the specific activity of the milk I^{131} content for a four-day period decreases exponentially. For patient 1 a minute trace of I^{131} was still found in the milk seven days after administration.

Thyroidal Uptake, Plasma Levels, and Urine Excretion of I^{131}.—All six patients were in the euthyroid range, although patient 1 was in the low normal range and has been given supplementary thyroid, with questionable benefit. The thyroid, plasma, and urine curves are produced here only for patient 1, (fig. 1), because this patient had the largest I^{131} milk excretion. For the six patients the 24-hour I^{131} thyroidal uptake ranged between 20 and 37% and the 24-hour urinary excretion of I^{131} between 46 and 65% of the dose administered. Balance calculations

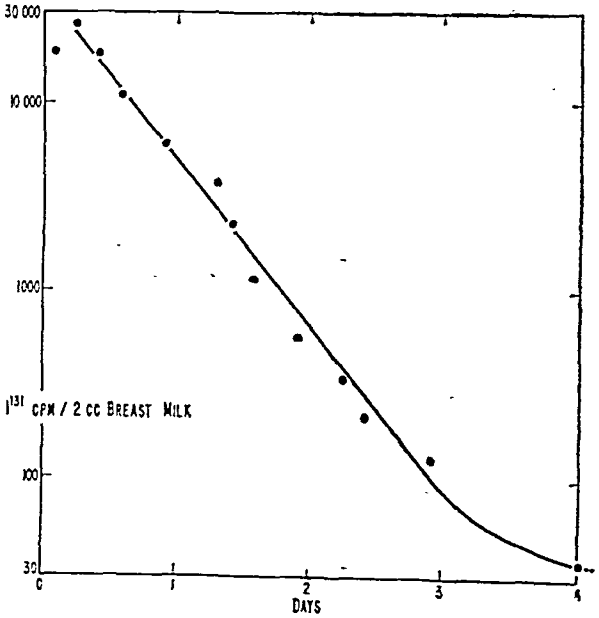

Fig. 2 (patient 1).—Curve on semilog paper showing decreasing concentration of I^{131} in breast milk.

at the end of 48 hours show the percentage of administered dose accounted for (thyroid, urine, and milk) to range between 90.0 and 100.4 (except for patient 6) (table 2). In all cases plasma levels of I^{131} at 48 hours were insignificant and did not amount to more than 1% of the total dose.

TABLE 2.—*Percentage of Administered Dose Excreted at End of 48 Hours*

Patient, No.	Thyroid Uptake, %	Cumulative Milk	Cumulative Urine	Total Accounted for, %
1...........	20	28.0	50	98.0
2...........	25	1.4	74	100.4
3...........	23	3.9	64	90.9
4...........	37	0.14	53	90.0
5...........	39	0.03	52	91.0
6...........	26	6.2	46	78.2*

* 24 hours only.

A comparison of the milk and urine content of I^{131} of patient 1 is of interest (fig. 1). For the first 24 hours the urine excretion was 46.0% of the ingested dose compared with a milk excretion of 23.3%. However, when based on percentage of ingested dose per liter of milk it is evident that roughly the same concentration was present in both (table 3).

In our patients with a small volume of milk production, the I^{131} concentration per liter was considerably less for milk than for urine. For example, patient 6 produced 0.395 liters of milk containing 6.2% of the administered dose of I^{131} (15% per liter) and 0.707 liters of urine containing 46% of the administered I^{131} (64% per liter).

Within 24 hours after I^{131} administration, most of the I^{131} that has not been concentrated in the thyroid gland has been excreted in the urine, leaving small amounts still in the blood stream. In addition, when there is a large milk production this becomes a major route of I^{131} exit from the body. When the milk production is small there is no increase in concentration of I^{131} in the milk, and perhaps a decrease, so the amount of I^{131} excreted in the milk is insignificant as compared with the urinary excretion.

Comment

A sizable percentage of orally administered I^{131} may be excreted in the milk. The quantity of milk produced is the important factor in determining the percentage of the administered dose that will be excreted by this route. If as much as 1 pt. is produced in 24 hours, the hazard to the infant might be considerable. Twenty-four hours after a tracer dose of I^{131} was given, Nurnberger and Lipscomb[1b] reported for one patient a thyroidal uptake of 34% and for her suckling infant a thyroidal uptake of 5%. For their second patient the uptake was 18% for the mother and 6% for the baby.

Miller and Weetch,[1d] on the basis of their calculations, concluded that a nursing infant might well receive a dose of 50 rep to the thyroid gland when the nursing mother had received 30 μc of I^{131}. We usually use a tracer dose of only 5 μc, and a dose to the infant thyroid gland of over 10 rep would be unlikely. Nevertheless, the inadvertent or thoughtless administration of radioactive material is not desirable, even though a dose of 10 rep would probably never seriously impair the function of the infant thyroid gland, nor does it seem likely that such a dose would be carcinogenic.

Since most of the milk excretion of I^{131} occurs in less than 12 hours, it would probably be safe for nursing to be resumed 12 hours after the dose is administered, but in order to allow for individual variation it would seem advisable to defer nursing until 24 hours after administration.

A small tracer dose administered to a nursing mother who is largely supplementing her infant's diet would probably be harmless for the infant. This would be particularly true of most of our group of patients, since the quantity of milk production was so small. For example, patient 5 produced only 17.8 cc. of milk during the 48-hour test period, and this contained only 0.033% of the administered dose. Since she was given 10 μc, the actual amount of I^{131} excreted was only 0.003 μc.

On the other hand, it is recognized that when hand stripping is substituted for infant nursing, the quantity of milk produced may be considerably diminished.[3] Since it is difficult to be certain that the milk production is actually small, it is certainly advisable to err on the side of conservatism and discontinue nursing during the test.

Since the plasma level curves are similar in all six patients, it seems evident that roughly the same amount of I^{131} was available for excretion into the milk for each patient for any given period of time. When there is a large milk output, carrying out considerable quantities of I^{131}, it is probable that some I^{131} is diverted from the thyroid gland, producing a lower gland uptake than that person would normally have. This possibility has been considered by Nurnberger and Lipscomb.[1b] Potter and Chaikoff[4] have presented experimental evidence for this lowering of thyroidal uptake by diversion of I^{131} into milk in their studies with lactating and nonlactating rats.

We have not analyzed the milk for hormonal I^{131}, but it has been shown that during the time of significant I^{131} milk content this iodine is not bound by protein.[1c] It may be that nursing mothers with hyperthyroidism might produce significant quantities of protein-bound I^{131} in the milk after treatment or a large tracer dose, but we have seen no data substantiating this.

TABLE 3.—*Comparison of I^{131} Excreted in Milk with That Excreted in Urine of Patient 1*

	Quantity of Urine, Liters	% of Administered Dose/Liter	Quantity of Milk, Liters	% of Administered Dose/Liter
1st 24 hr. . .	1.318	34.8	0.642	37.1

Summary and Conclusions

Milk excretion of orally administered I^{131} was measured in a group of six euthyroid lactating women. The concentration of I^{131} in the maternal milk will often be sufficiently high to be potentially hazardous to the child. The I^{131} appears in the milk within a short time after administration, and most of the I^{131} that is excreted in the milk appears during the first 12 hours, although small, continually diminishing amounts of I^{131} appear in the milk for many days. In none of these patients was the amount in the milk significant after 24 hours.

The specific activity of I^{131} in the milk (percentage of administered dose per liter of milk) showed a certain amount of variation for all these six patients, although the specific activity was less when the volume of milk production was small.

The percentage of administered dose of I^{131} excreted in the milk is roughly in proportion to the quantity of milk produced. The greatest hazard to the nursing infant will occur when the mother is supplementing little or not at all and because of this produces large quantities of milk. Therefore, technicians should routinely ask any woman of childbearing age whether she is lactating, and, if so, nursing should be discontinued for at least 12 and preferably 24 hours. If the tracer dose is over 30 μc, or if it should be necessary to administer a therapeutic dose of I^{131}, nursing should not be resumed until measurements indicate an insignificant milk content of I^{131}.

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Mrs. Gretchen Fox gave technical assistance in this study.

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ERYTHEMA NODOSUM IN PRIMARY HISTOPLASMOSIS

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Erythema nodosum was the primary complaint in two children (a girl aged 2 and a boy aged 2¾ years) and was found secondarily in connection with other problems in two other children (a girl aged 6½ and a boy aged 7½ years). In all four cases the skin tests for tuberculosis gave negative results but reactions to histoplasmin were strongly positive. In no case was there evidence of rheumatism. It seemed evident that the erythema nodosum was a manifestation of histoplasmosis. In regions known to harbor Histoplasma capsulatum this organism must be considered among the possible causes whenever the physician deals with a fever of undetermined origin.

Erythema nodosum is an allergic response clinically associated with certain disease states, of which tuberculosis, streptococcic infection, and rheumatic fever have been most often described. The earliest report was in 1808, by Willan, who noted the eruption in his book, "On Cutaneous Diseases." Its association with rheumatism was soon noted, then with tuberculosis. Other infections and drugs, notably sulfathiazole, have been reported as causing erythema nodosum.[1]

In 1932 Collis [2] described the clinical relationship between erythema nodosum and allergy to tuberculin or to a streptococcic "endotoxin." Shortly thereafter, Dickson [3] related the occurrence of this skin manifestation in patients with coccidioidomycosis to the time when their sensitivity to coccidioidin was at its greatest. Thus, bacterial, mycobacterial, and mycotic infections have variously been indicated as being related to erythema nodosum. It should be noted that geographical differences have been marked in the various series of cases reported.[1]

Although the occurrence of erythema nodosum in patients with primary histoplasmosis in geographical areas where this infection exists is not surprising, reports on it in the literature are scanty; we have noted this association since 1953. Dublin and associates [4] reported the case of an adult with proved histoplasmosis and with "bluish, erythematous-roughened, cutaneous areas of the knees," diagnosed as seborrheic dermatitis on the basis of a biopsy specimen. In 1950, Heilbrunn and Cain [5a] reported on a patient with pulmonary histoplasmo-

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sis, erythema nodosum, and arthritis. In 1954, Dickie and Murphy,[5b] and in 1956, Nuttall-Smith,[5c] called attention to this relationship in individual case reports. We should like to report and comment on this association in four children.

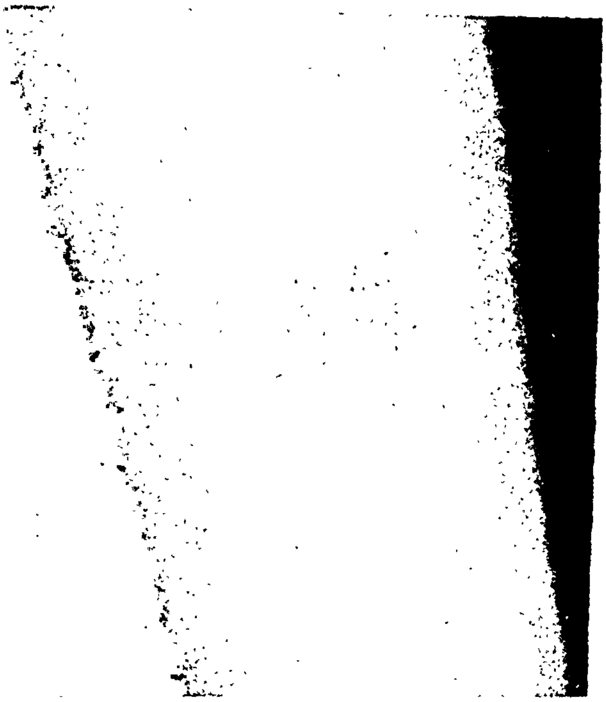

Fig. 1 (case 1).—Erythema nodosum in primary histoplasmosis: photograph showing positive result of histoplasmin skin test.

Report of Cases

Case 1.—A 6½-year-old girl was referred to the Children's Hospital because of a pulmonary lesion seen on x-ray films. The child's progress had been followed for five years with tuberculin skin tests and roentgenograms taken every six months after the mother was found to have "open tuberculosis." About six months previously, the child's chest x-ray had been noted to appear suggestive of tuberculosis, but the result of her tuberculin skin test remained negative. Physical examination was not remarkable. She was given skin tests with Old Tuberculin (OT), in 1:1,000 dilution, and with histoplasmin in 1:100 dilution. Two days later, the result of the histoplasmin skin test was markedly positive (fig. 1) and the tuberculin reaction was negative. It was noted that the left side of the child's forehead had become swollen and erythematous, with a vesicular center. The left periorbital area was also swollen and the left upper lid erythematous. There was another 1.5-cm. area of indurated erythema on the right side of the forehead (fig. 2). These areas were mildly pruritic but nontender. They disappeared in two days, but similar lesions reappeared on the forehead and left wrist four days later. She was seen three years later, when the reaction to a recheck purified protein derivative (PPD) skin test (5 tuberculin units) was still negative, as were findings of the chest x-ray.

Case 2.—A 2-year-old girl with a three-day history of painful pretibial nodules was referred to the Children's Hospital. The patient recently had been in contact with two persons with active cases of pulmonary tuberculosis. The examination was not remarkable save for painful erythematous nodules on both legs. Skin tests gave a negative result with PPD (5 tuberculin units) and a strongly positive reaction to histoplasmin. The corrected erythrocyte sedimentation rate showed a 28 mm. fall in one hour (Wintrobe), and the white blood cell count was 16,400 per cubic millimeter, with a mild shift to the left. The chest roentgenogram showed no abnormalities. Serum tested for histoplasma complement-fixation proved to be anticomplementary. The skin lesion disappeared in seven days.

Case 3.—A 7½-year-old boy had developed a "flu-like picture" eight days before admission, with fever, sore throat, and generalized aching. A "fever blister" of the lip had developed at about the time of onset and next, four days before admission, he complained bitterly of pain below the knees. Shortly thereafter, the typical eruption of erythema nodosum was noted. Except for these lesions, which had persisted, and a reddened pharynx, the result of physical examination was normal. His white blood cell count was 11,400 per cubic millimeter, with a mild shift to the left and a corrected erythrocyte sedimentation rate of 32 mm. by the Wintrobe method. On chest x-ray, an enlarged lymph node at the tracheobronchial angle on the right was noted. Results of skin tests with PPD (5 tuberculin units) were negative and strongly positive with histoplasmin. Because of the pharyngitis the patient was treated with penicillin, but his temperature which, on admission, had been 102 F

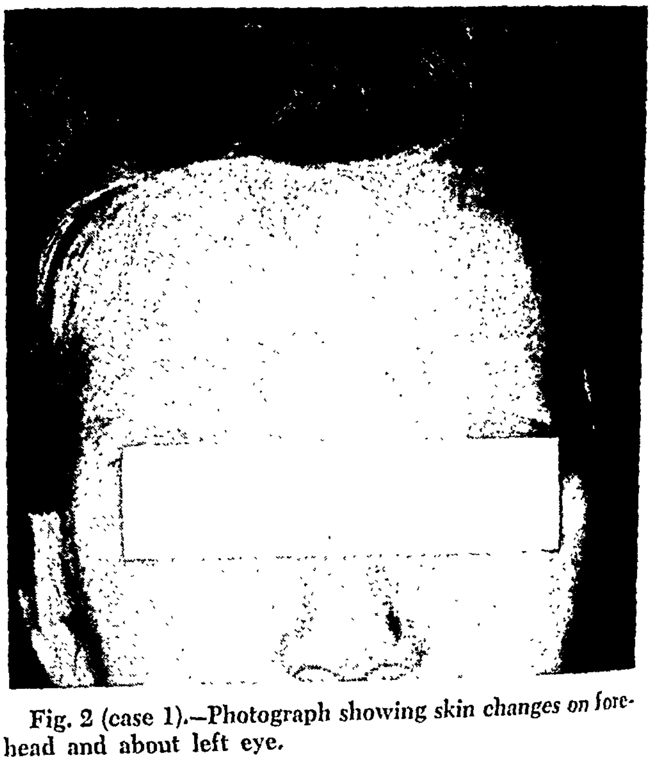

Fig. 2 (case 1).—Photograph showing skin changes on forehead and about left eye.

(38.9 C) only gradually fell to normal by the fifth day. The skin lesions disappeared in 14 days.

Case 4.—A 2¾-year-old boy was referred to the Children's Hospital because of the sudden occurrence of lesions on the legs typical of erythema nodosum. One week before admission he had developed an intermittent, low-grade fever and had become anorectic; the mother then gave the child tetracycline. No improvement occurred, and he was taken to his physician, who prescribed an anthelmintic. Two days later the eruption developed. Administration of the drugs was discontinued and the child was hospitalized. Physical examination was not remarkable except for the bilateral erythema of the anterior lower limbs. Routine skin tests revealed a strongly positive reaction to histoplasmin and a negative one for PPD (fig. 3). The white blood cell count was 8,600 per cubic millimeter, with a normal differential count. A specimen of the patient's serum was tested by Heiner[6] and reported to be indicative of active histoplasmosis. The chest x-ray revealed a patchy infiltrate in the right side of the chest. No therapy was given, and the skin and pulmonary lesions regressed in one week.

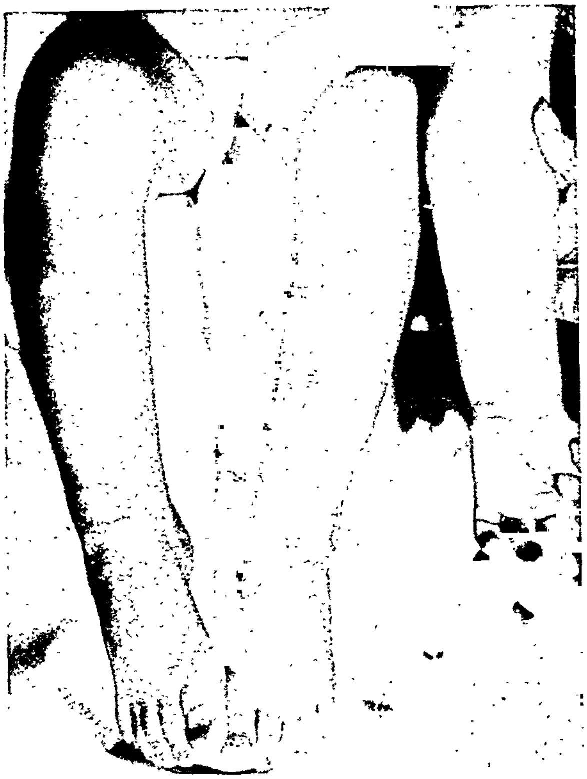

Fig. 3 (case 4).—Photograph showing typical lesions of erythema nodosum and positive reaction to histoplasmin skin test.

Comment

The cause-and-effect relationship between primary histoplasmosis and erythema nodosum in the four children reported by me seems obvious. The tuberculin reactions were negative; there was no evidence of rheumatism; and the area in which the hospital is located is free of coccidioidomycosis. Furthermore, in case 4 the result of the newly described precipitin-in-agar-gel test of Heiner[6] (in conjunction with the pulmonary lesions and the positive result of the histoplasmin skin test) indicated active infection with Histoplasma capsulatum. Although the question of hypersensitivity to the anthelmintic and the antibiotic given to the patient in case 4 can be raised, one would not expect these drugs to cause skin reactions like those to histoplasmin and to produce serum precipitins.

A review of the cases of erythema nodosum seen at either the Children's Hospital or the Louisville General Hospital in the past six years disclosed a total of 11 patients. The underlying cause apparently was acute rheumatic fever in two (Jones' criteria[7]), primary histoplasmosis in four, and not established in five. The result of a histoplasmin skin test performed on one of the latter patients was negative; none was given to the other four. Findings of chest x-ray in four cases were noncontributory, and none was made in one instance.

In regions known to harbor endemic histoplasmosis, the benign form of this disorder is not unusual. In my experience it must always be considered a cause of fever of undetermined origin. The availability of various confirmatory serologic tests, as noted by Heiner,[6] has helped to resolve numerous diagnostic puzzles. Sensitivity to Histoplasma capsulatum should be considered in any child with erythema nodosum.

Summary

In four children, whose cases are reported, a relationship between primary histoplasmosis and erythema nodosum was established. Geography plays a role in the etiology of erythema nodosum.

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J.A.M.A., June 25, 1960

SURGICAL MANAGEMENT OF FOCALIZED PULMONARY HISTOPLASMOSIS

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Fifty-seven patients underwent surgical removal of a pulmonary histoplasmoma because the possibility of malignancy could not be excluded without thoracotomy. The surgeon must orient himself before the operation, for the patient with histoplasmosis is usually asymptomatic, while the thoracotomy sometimes leaves residual discomfort that outweighs previous complaints. The histories of five patients, all men between the ages of 18 and 40 years, illustrate the course of the disease and the results of surgery. There were no characteristic findings at operation which specifically identified the histoplasmoma; the diagnosis was made by identifying Histoplasma capsulatum in the excised nodules. The average hospital stay for the 57 patients was 158 days. Of those whose progress was followed up for two to seven years after operation, only three reported major respiratory complaints.

Surgical considerations in histoplasmosis are of recent date and are becoming increasingly significant. The clinical entity of histoplasmosis was first reported by Darling[1] from Panama in 1906. The second observers, Riley and Watson[2] of Minnesota, made their report 20 years later. As recently as 10 years prior to the time of writing, Hodgson, Weed, and Clagett[3] were able to collect only 123 cases. In 62 of these there was pulmonary involvement. They reported one patient on whom they had carried out pulmonary lobectomy, and they believed this to be the second patient on whom pulmonary resection had been performed. Sporadic case reports have since been published concerning surgical therapy.[4] Davis, Peabody, and Katz[5] emphasized the importance of histoplasmosis as a cause of the solitary pulmonary nodule.

The extensive epidemiologic studies of the past decade have led to the demonstration that infection with the causative organism, Histoplasma capsulatum, is extremely prevalent. In fact this disease, considered rare a few years ago, is now believed to infect millions of persons in the United States.[6] Recently, refined and improved staining techniques have permitted the experienced observer to recognize these organisms in diseased tissue with relative ease, and the diagnosis of histoplasmosis is becoming commonplace.[7]

This presentation deals with 57 patients on whom operations were performed during 1951 to 1957. It is neither a selected group, nor does it represent a consecutive series of patients; rather, it is a relatively large group on whom certain data are available. The medical and surgical management have been a combined effort of members of the staffs of several Army hospitals, and credit to all persons who have contributed is gratefully acknowledged. This report is confined to an interesting phase or manifestation of this disease, representing a focalization of the process in the lung. Generally, the patients being reported were not ill, though there are varying degrees of exceptions. The detection of an abnormal shadow on the chest roentgenogram as a rather rounded area of increased density alerted the physician to the need for further investigation. Briefly, the investigations did not establish the cause of this abnormal shadow and led to exploratory thoracostomy.

The operation performed was usually the removal of a single or of the larger of multiple nodules with an adjacent portion of lung tissue, with or without removal of mediastinal lymph nodes. The diagnosis was not proved until the histological examination of the removed tissue demonstrated the presence of H. capsulatum and the absence of other possible etiological causes. This is an oversimplification of the problem but allows a base line for the variations which are encountered.

Report of Cases

Case 1.—A caucasoid male soldier, aged 18 years, had had poliomyelitis at 9 years of age. He made a splendid recovery without residual effects except for moderate talipes cavus of his left foot. An appendectomy had been performed at 13 years of age. His general health had been excellent.

Ten days prior to admission to an army hospital in April, 1957, he had been treated for a streptococcic sore throat. The day before admission he had symptoms of generalized muscle aches, especially in his arms, nausea and vomiting, and headache. These complaints caused him to be hospitalized. His temperature was 101.6 F (38.5 C); respiration rate 20 per minute, and blood pressure

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reading 110/60 mm. Hg; except for the talipes cavus of the left foot, results of the general physical examination were normal. He recovered within a few days from this acute illness.

The chest roentgenogram made at this time revealed slight generalized haziness and two rather distinct areas of increased density, one in each lung field and each measuring roughly 2 by 3 cm. in diameter. A roentgenogram of the chest made four months earlier, at which time he had been asymptomatic, was reviewed and showed the same areas of increased density to be more clearly defined. A thorough evaluation including intravenous pyelography, long bone survey, and histological study of removed scalene lymph nodes and fat tissue was negative for evidence of neoplastic disease. A diagnosis of pulmonary tuberculosis was considered but ruled out because of repeated negative results from sputum cultures and a negative result from a tuberculin skin test. The findings from the coccidioidin skin test were negative, but the result of the histoplasmin skin test was 3+. He was discharged from the hospital and given instructions to be examined at his new station assignment.

Four months later, in August, 1957, the patient was reevaluated. He felt that he had noted some increased "tightness" in his chest on strenuous exercise since being told about the findings noted on his chest roentgenogram. His general physical condition had remained excellent, and findings of his physical examination were unchanged. This study revealed no findings which shed further light on an accurate diagnosis of the nodular lesions still noted and unchanged on the chest roentgenogram. It was recommended that the patient be transferred to Walter Reed General Hospital for consideration of surgical removal of one of the nodular lesions.

The evaluation at Walter Reed led to concurrence in the recommendation for exploratory thoracostomy. This was carried out on the left, and a -cm. hard lesion was palpable in the substance of the anterior segment of the upper lobe. Throughout the remainder of the upper lobe were several lesions measuring 2 to 3 mm. The larger lesion with wide margin of surrounding lung tissue was excised. The examination of the cut section of the gross specimen revealed the nodule to be about cm. in diameter, laminated, firm, and well encapsulated. Organisms identified as H. capsulatum were present in the removed nodule. There was no evidence of neoplastic disease or tuberculosis. The patient made an uneventful recovery and returned to duty. Two years later, at the time of writing, he states that he considers himself in good health. He is on duty in Germany.

Case 2.—A 20-year-old caucasoid male soldier came under medical observation because a chest roentgenogram made in connection with his request in July, 1953, for duty with airborne troops revealed enlargement and lobulation of a large area of right hilar density (fig. 1). Linear markings extended peripherally to an ill-defined rounded density at the level of the 4th intercostal space. Thorough studies did not clarify the causative nature of the above findings. He was not ill and had no complaints.

Results of the coccidioidin and the tuberculin skin tests were negative, while the findings of the histoplasmin test were positive. Exploratory thoracostomy was recommended and was performed in October, 1953. The surgical operative findings revealed a few scattered rounded subpleural nodules throughout the right lung. The larger nodules were estimated to be about 1 cm. in diameter. A wedge excision of a larger pulmonary nodule was performed, and partial excision of a much enlarged densely adherent tracheobronchial lymph node was accomplished. The histological examination demonstrated H. capsulatum in the lung tissue but no organisms in the fibrocaseous lymph node. The patient made an uneventful recovery, returned to duty, and continued in excellent health until he was fatally injured five months later in an automobile accident. Autopsy findings revealed scattered small tubercles in the liver, spleen, lungs, and mediastinal lymph nodes. H. capsulatum was identified in the spleen, lung, and mediastinal lymph nodes. It is probable that the lesion in the liver was also due to histoplasmosis, but this was not confirmed. The organisms had not been identified in the lymph tissue removed at the time of operation. We do not believe that this represented dissemina-

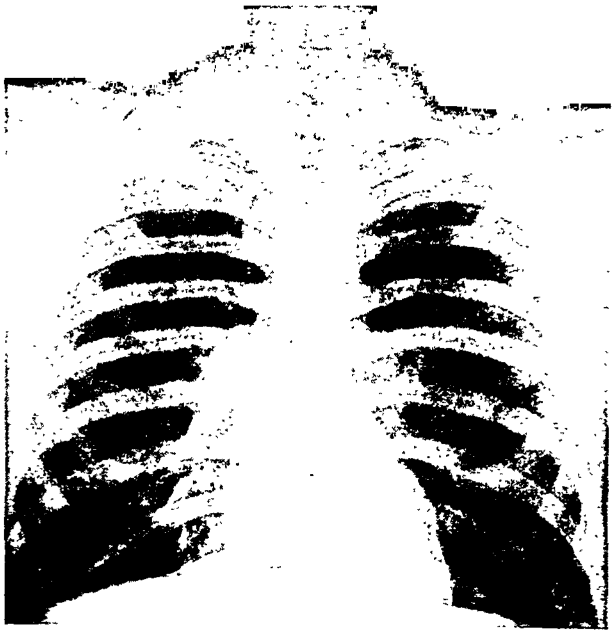

Fig. 1 (case 2).—Enlarged area of increased density of right hilus with linear markings to indistinct rounded area in fourth intercostal space.

tion after surgery; rather, the process was considered already present but did not produce symptoms.

Case 3.—A 36-year-old Army officer had a histoplasmoma removed from the right lower lobe in November, 1956. Findings from the tuberculin and coccidioidin skin tests were negative. The result of the histoplasmin skin test was positive. The chest roentgenogram of Sept. 21, 1956, revealed an indistinct lesion in the right lower lung field. An overexposed film and the lateral projection revealed a distinct 2.5-cm. rounded lesion in the right lower lung field (fig. 2). Pleural fluid accumulated postoperatively, requiring performance of thoracentesis on three occasions. Two and one-half years postoperatively the patient states that his general health is good and that he has no complaints referable to his chest.

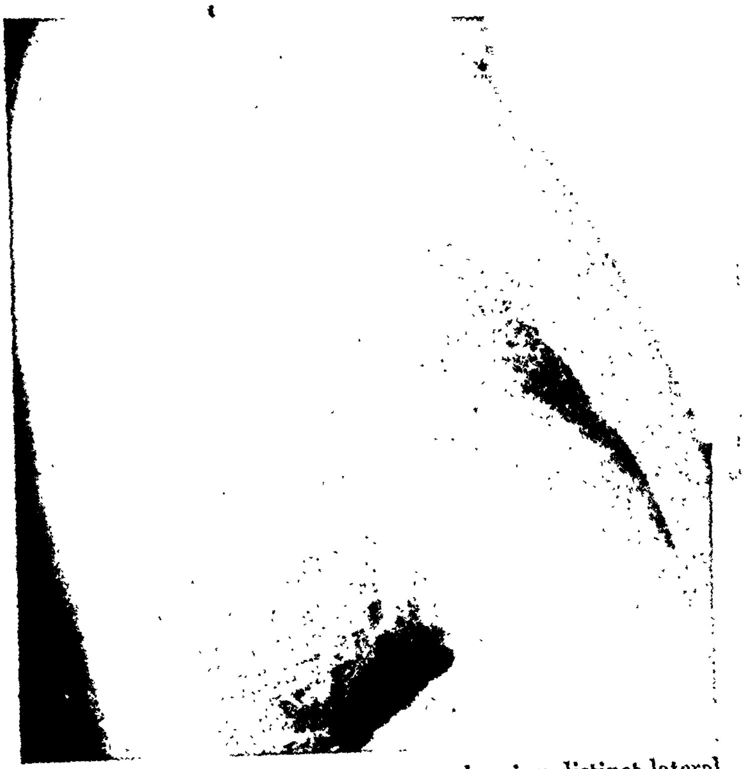

Fig. 2 (case 3).—Roentgenogram showing distinct lateral projection lesion.

Case 4.—In the course of clinical investigation and treatment of a 40-year-old man for bronchial asthma in May, 1957, a chest roentgenogram revealed an area of multinodular increased density in the left lower lung field. This finding led to exploratory thoracostomy and the operative removal of a mass in the lung which, on cut section, was 3.5 cm. in diameter. It consisted of multiple smaller nodules and had a soft caseous center. Interesting findings were noted on reviewing previous chest roentgenograms. The roentgenogram made in April, 1952, may have suggested increased density of the left hilum but did not delineate the area of involvement in the left lower lobe. In 1956 the area of involvement was clearly defined on the film, and in 1957 the multinodular nature of the density was revealed. The lesion is posterior. Two and one-half years postoperatively the patient attributes improvement of his asthma to the surgical removal of the histoplasmoma (fig. 3).

Case 5.—A 36-year-old caucasoid male Army officer came under medical observation at Walter Reed General Hospital on Dec. 18, 1957, because a rounded area of increased density was noted in the right lower lobe on a routine chest roentgenogram. A thorough clinical work-up several days earlier had not revealed a causative agent for this abnormal shadow and exploratory thoracostomy was advised. A single hard 2.5-cm. lesion was present in the right lower lobe and was removed with a wide margin of adjacent lung tissue. The fibrocaseous nodule contained H. capsulatum. The patient left the hospital 10 days after the operation and returned to duty one month later. Several chest roentgenograms made a few years earlier and considered negative for pathological lesions were reexamined in the light of the present findings. O the 1951 and 1953 roentgenograms an area o increased density at the same site was noted. This appeared larger in 1955 and 1957 and led to exploratory thoracostomy. He has remained well. The gross and microscopic findings of a histoplasmoma and the specific organism, H. capsulatum are depicted in figures 4 and 5.

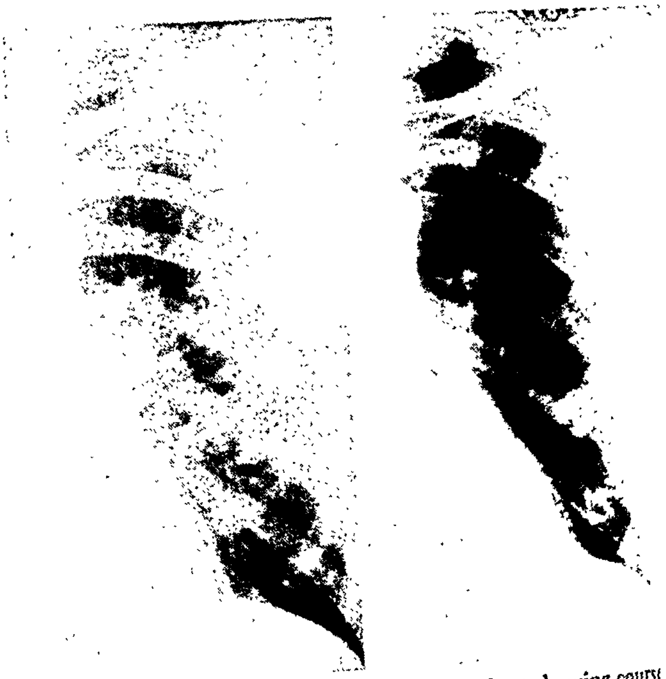

Fig. 3 (case 4).—Roentgenograms of chest showing cours of development of histoplasmoma over five-year period. Left, April 23, 1952. Right, Feb. 5, 1957.

The incidence of this series represents that o military personnel with an average age of 33 years The youngest patient was aged 18 and the oldes 62 years. Only two patients were over 50 years o age. There were only six women in the group of 5 patients. They were all caucasoid.

The areas of residence of these patients reflec the wide geographical distribution of the member of our Armed Forces. The fact that nearly 30% had resided, several months or years, in Panama may again focus attention to the area of the original detection of clinical histoplasmosis. The east central states, New England, the Middle West, and the Pacific coast areas all are significantly represented as places of residence of the patients in this group.

The skin test for histoplasmosis is, we believe, significant. Only 1 of the 52 patients skin tested with histoplasmin gave a negative reaction. The result of the coccidioidin skin test was positive in 1 of every 4 of the 44 patients so tested. The findings of the tuberculin skin test were negative in only 12 of the 52 patients tested. These observations strongly suggest that a negative result from a histoplasmin skin test practically rules out a focalized pulmonary lesion due to histoplasmosis. Our experience with serologic tests is too limited to warrant a comment as to their usefulness in surgical consideration.

The differential diagnosis of focalized pulmonary histoplasmosis embraces the long list of lung lesions such as granulomas, certain infectious processes, the neoplastic diseases, filled pulmonary cysts, encapsulated pleural effusion, empyema, and several other less common conditions. Its close simulation to tuberculosis is readily apparent when one notes that about one-half of the patients in this group were treated for lengthy periods with antituberculosis drugs before surgical exploration led to the establishment of the nontuberculous etiology. More than 75% of the patients in this group were operated on before 1955, and during this period tuberculosis was by far the most generally, though erroneously, accepted etiological factor producing the roentgenographic findings noted in focalized pulmonary histoplasmosis.

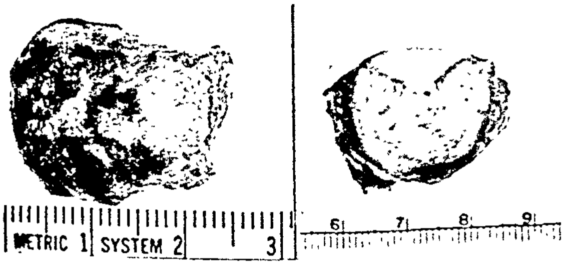

Fig. 4 (case 5).—*Left,* pulmonary tissue containing histoplasmoma. *Right,* histoplasmoma showing lamination and puckering of pleura.

Comment

There are no characteristic findings at operation which specifically identify the histoplasmoma. Palpation of the lung enables one to detect the general extent of the main nodule and often the presence of small, even minute satellites or additional nodules. The high prevalence of multiple lesions emphasizes the likelihood of histoplasmosis. Adhesions are seldom significant, but there is an occasional marked exception. The visceral pleura overlying the main or larger nodule was often thickened and puckered. The largest nodule did not, in this group, exceed 4 cm. in diameter. Only 20% had a diameter of 3 cm. or more and the average measurement was 1.8 cm. Except for four lobectomies, segmental resection or wedge excision was the surgical procedure performed. The main or larger nodule usually had a firm or rubbery consistency, though it occasionally was semifluctuant. The cut surface revealed a dense fibrous wall, often with a laminated periphery and a soft center. Cavitation of the focalized lesion is, in our experience, rare. However, it is estimated that about 3,000 patients with cavitary pulmonary histoplasmosis are hospitalized in the United States, whose cases generally are undiagnosed.[8] Regional lymph nodes were variable in showing gross abnormalities. The focalized lung lesions were grossly indistinguishable from similar granulomas due to Mycobacterium tuberculosis or Coccidioides immitus.[9]

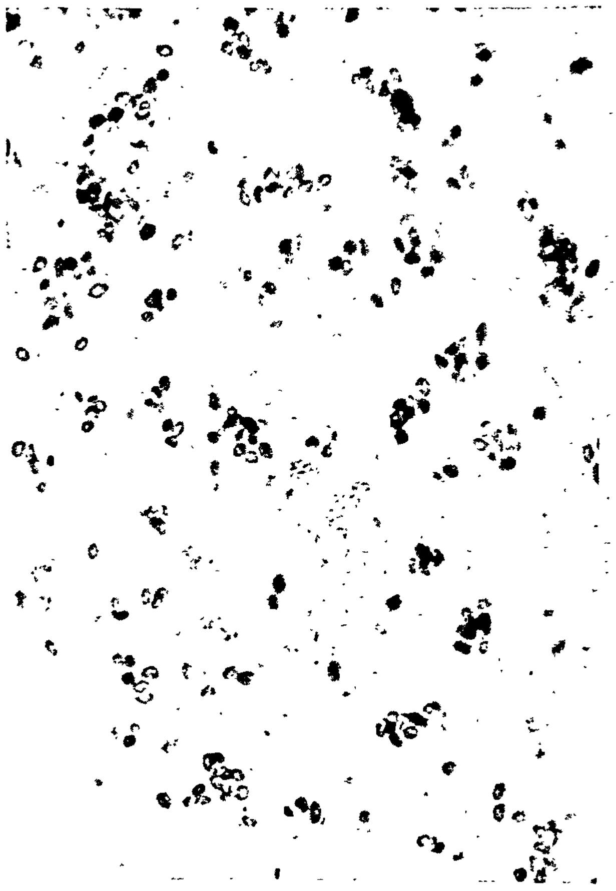

Fig. 5 (case 5).—H. capsulatum shown in pulmonary nodule.

A significant observation which this study supports is the present application of the earlier surgical approach in establishing the diagnosis. Prior to 1953, when Puckett [10] called attention to the presence of H. capsulatum organisms in a group of 22 surgically resected pulmonary nodular lesions, it was usual to classify these as tuberculomas, implying a tuberculous etiology. The present earlier application of surgical removal of these lesions which results in a marked reduction in hospital stay is based on two reasons: first, the recognition of the histoplasmoma as a distinct lesion of specific etiology; second, the inability to distinguish it from neoplastic disease makes it urgent that it be removed immediately. The average hospital stay in this group of 57 patients was 158 days. During the past two and one-half years we have reduced this average by 76%, eliminating three of every four hospital days, in the 24 patients treated surgically at Walter Reed General Hospital.

The time interval between the detection of the focalized lesion in the lung and its removal has such extreme variables, in fact, days to years, as to be of limited value in formulating recommendations for its removal. The aid gained from the repeated study of earlier chest roentgenograms may be valuable. However, the presence of the undiagnosed lesion makes it difficult to recommend that it not be removed. A protracted hospital stay for study, rest, or drug therapy is not now considered advisable. If the findings and diagnosis reveal something other than histoplasmosis, appropriate therapy is indicated.

This dictum does not, however, always resolve itself so readily. These patients are often not ill, having few, if any complaints, and if they do not feel as well or better after than before surgery it may be apparent to them, if not also to the doctor, that their conditions have not been improved. This then requires a thorough preoperative orientation of the patient by the surgeon as to the reasons for surgical intervention and what may be expected on a long-term basis after operation if the disease proves to be histoplasmosis.

The complications attending the operation in these 57 patients were of major significance in two patients. One required upper-phase thoracoplasty to obliterate an air space. The other patient developed a pulmonary hematoma requiring removal of the basal segments of the left lower lobe. Four patients required thoracentesis on more than one occasion, and in one patient a chest wall abscess developed at the operative site requiring incision and drainage four months after operation. H. capsulatum was identified in the contents of the abscess.

Inquiry was made concerning the present status of health of the 57 patients two to seven years after operation. This could not be ascertained in three patients. One patient (case 2) was fatally injured five months after operation. Of the other 53 patients, 43 considered themselves to be in good health and had no significant complaints referable to their chests. Ten patients considered their conditions fair. This latter evaluation in the light of the rather frequent chest discomfort which often persists after intrathoracic operations may not be entirely appropriate. They note varying degrees of chest pain, and one complained of numbness on the operative side seven years postoperatively. Five of the ten patients are on active military duty; three are overseas. One patient is, and was at the time of operation, undergoing psychiatric therapy. Her complaints are vague and do not permit accurate interpretation. One other patient indicated no specific complaints.

Only three patients appear to have problems of major significance. Two had a long history of respiratory complaints. At operation both had marked adhesive pleuritis. One patient had been undergoing rest and drug therapy for pleural effusion for 18 months prior to operation. During this period he also had a laminectomy, with the removal of a herniated nucleus pulposus. It is doubtful i the finding of a histoplasmoma and its operativ removal had substantial importance as a causativ factor of his pulmonary and pleural disease or o his present complaints. This patient is on activ military duty.

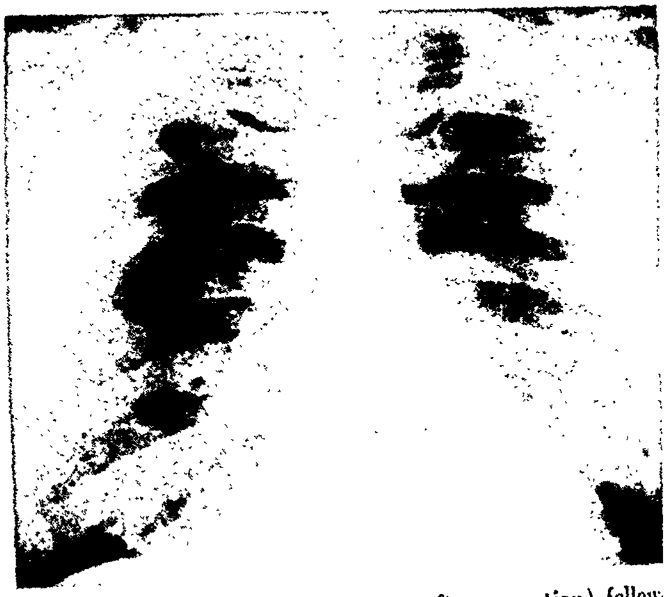

Fig. 6.—Long-term (seven years after operation) follow-up chest roentgenogram of patient who had histoplasmoma.

Two patients have probably had reactivation o their pulmonary disease and may more properl fit into the classification of the type with chroni progressive disease. The relationship to the removal of the histoplasmoma is indeterminable. On person was well and reenlisted two years afte surgery and remained well for a total of near four years before showing mild symptoms of progressive disease. The other patient had seve asthma, and about three years after removal of a atelectatic right upper lobe containing numerou organisms results of a sputum culture were positive for H. capsulatum. The patient was then hospitalized for two months. The long-term appea ance of the chest roentgenogram after removal of a histoplasmoma is depicted in figure 6.

Focalized pulmonary histoplasmosis is becoming of increased surgical significance. The undiagnosed rounded shadow often noted on the chest roentgenogram presently requires surgical removal of the lesion for definite histological diagnosis. A high percentage of such lesions are manifestations of histoplasmosis. After such a diagnosis is thus established, there seems to be no evidence that the patient requires hospitalization beyond the period of recovery from the surgical procedure. Also, the period of study and the hospital stay prior to operation should be brief. If the diagnosis proves to be other than focalized histoplasmosis, appropriate therapy is, of course, indicated.

The experiences encountered in the surgical considerations of 57 patients have revealed certain interesting information. The disease process is not limited to any particular geographic area. Residence in Panama may be of significance in indicating a higher likelihood of developing focalized pulmonary lesions. All patients in this group were caucasoid. The average age of the patients was 33 years. The result of the histoplasmin skin test is believed to be highly significant and was negative in only 1 of 52 patients tested. The differential diagnosis remains largely an academic appraisal requiring histological proof. Because the patient is generally not ill prior to operation, careful orientation of the patient by the surgeon is required in indicating the need for surgical intervention to establish the diagnosis. The frequently encountered sequelae of discomfort in the chest after intrathoracic operations should not be unduly minimized to the patient. If he knows beforehand what to expect, he is less apt to magnify the usual minor complaints. This follow-up study reveals two questionable instances of reactivation of the disease three and four years, respectively, after surgical removal of a histoplasmoma. These may more properly be classified under the chronic progressive type of histoplasmosis. Until more reliable means are available, it appears to be generally necessary to surgically remove the focalized pulmonary histoplasmoma to prevent the lesion from growing.

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SIR ASTLEY COOPER.—Probably the man who was responsible above all others for making Guys a famous institution was the great surgeon, Sir Astley Cooper—of whom some one said at that time that next to the king, he was the best-known man in England. He spent much of his time every day at Guys, dissecting, operating, and lecturing, and his popularity with the Borough-School pupils was unbounded. His private practice was enormous, but it was never allowed to stand in the way of his hospital work. He rose every morning at daybreak and spent two hours before breakfast dissecting. It was usually midnight before he had finished his round of professional visits. Often, when his private consulting rooms were overcrowded, he would leave by the back door for his beloved Guys and even then, it was said, patients sometimes followed his coach through the streets.—W. A. Wells, A Doctor's Life of John Keats, Vantage Press, New York, 1959, page 71.

DIET IN CORONARY ATHEROSCLEROSIS

Lester M. Morrison, M.D., Los Angeles

The nutritional approach to the treatment of atherosclerosis was tested in 100 patients with proved coronary atherosclerosis. Fifty patients were treated with a low-fat, low-cholesterol diet. The other 50 patients were not given any specific treatment and acted as controls. By the end of 12 years, 19 of the 50 patients treated with the diet survived. Of the 50 control patients, all had died by the 12th year of observation. The total daily fat intake in this diet was 25 Gm. Animal fats were eaten in minimum quantities. Large-scale trial under controlled statistical conditions encountered in clinical practice is suggested for further evaluation of the role of fat in coronary atherosclerosis.

Atherosclerosis is now recognized as the hallmark of the American way of life, since it already has been shown to afflict about 77% of American males as early as in the 20-to-30-year age range.[1] Cholesterol is the *sine qua non* of the atheromatous lesion. This lesion heralds the role of atherosclerosis in the production of coronary thrombosis, cerebral thrombosis, and other atherosclerotic complications later in life, to the extent that it is responsible for most death and disease in the adult American population.

Current medical research has indicated the following causative factors in atherosclerosis: heredity, disorder in lipid metabolism, diet, unknown factors within the arterial walls, endocrine and enzymatic disturbances, stress, and disturbance in vascular clotting. Treatment along medical lines has been characterized by attempts to correct demonstrable abnormalities noted in the blood such as thyroid deficiency in hypothyroidism; correction of abnormalities in blood lipids, notably cholesterol, as found particularly in patients with familial hyperlipemia, hypercholesteremia, or both, with or without xanthomas; and diabetes mellitus accompanied by excessive cholesterol, lipid, or triglyceride blood levels. In particular, hypercholesteremic patients or persons with proved or suspected coronary atherosclerosis, such as those with past myocardial infarctions, angina pectoris, or arteriosclerosis obliterans of the lower extremities, have been treated with the intent of reducing any existing blood cholesterol or lipoprotein (or both) elevations. Persons with familial histories of myocardial infarction, coronary atherosclerosis, or hypertensive cardiovascular or cerebrovascular disease are now often treated preventively,[2] with the aim of correcting blood cholesterol or lipoprotein abnormalities, or both, in the hope that prophylactic measures will reduce, postpone,or avoid statistically likely coronary or cerebral thrombosis of atherosclerotic origin.

Many reports[3] now exist on the effectiveness of low-cholesterol or low-fat diets in reducing abnormal blood cholesterol or lipoprotein levels. The recent study by Brown and Page[4] demonstrated that the reduction of serum cholesterol levels to or near normal in hypercholesteremic subjects was achieved by either a low-fat, low-cholesterol diet or the vegetable oil dietary pattern used by the authors. Serum cholesterol levels fell within a few days or weeks with either type of diet. In some subjects the cholesterol level was lower with the vegetable-oil dietary pattern than with the low-fat, low-cholesterol diet, and in all subjects it appeared to be more steady.

The results were confirmed by the published observations that moderate reduction of saturated fats in the diet, as with a low-fat, low-cholesterol diet, produced significant lowering of plasma cholesterol levels in human subjects with hypercholesteremia. The effect was consistent in all of a series of subjects studied, although the response was variable. Each subject had a significant decrease in plasma cholesterol level while receiving the low-fat, low-cholesterol diet alone.

Although there is an abundant literature, expressing the view that dietary cholesterol content in man has little, if any, influence on serum cholesterol levels,[5] the most definitive and recent investigation by Beveridge and associates[6] has clarified this question effectively and conclusively. These authors found that the serum cholesterol level in man is highly responsive to the concentration of dietary cholesterol. On the basis of these experiments there can no longer be any doubt of the responsiveness of man to dietary cholesterol, although the nature of the accompanying fat or oil affects to a large extent the response obtained. In a series of 93 university students it was found that when cholesterol per se was fed to 8 groups in amounts varying from 25 to 1,000 mg. per 950 calories, the serum cholesterol values were found to increase to between 200 and 400 mg. per 950 calories or 600 to 1,200 mg. daily. At dietary cholesterol levels of above 400 mg. per 950 calories, the serum concentration of the sterol reaches a plateau.

From the Medical School, College of Medical Evangelists, and the Crenshaw Hospital.

There are a few reports on the effects of a low-fat, low-cholesterol diet on the mortality and morbidity of persons with proved coronary atherosclerosis, as evidenced by myocardial infarction.[7] These reports are of relatively short periods of observation over several years. The following data are from the first long-term study of the effects of such a diet over a 12-year period of observation.

Clinical Material

In 1946 I began the study of 50 patients to determine the relationship of dietary fat intake to the incidence of atherosclerosis.[8] This series was compared to an alternate series of 50 patients with proved coronary atherosclerosis who were on the "normal" or usual American dietary intake of cholesterol and fat for three-years.[8a] One hundred consecutive patients with recent proved coronary thrombosis and myocardial infarction were thus observed for a three year period. Eighty-six men and 14 women, whose ages ranged from 32 to 70 years, were studied. No patients were included whose systolic pressures exceeded 180 mm. Hg or whose diastolic pressures exceeded 110 mm. Hg. No other disease such as hypertension, diabetes mellitus, nephritis, thyroid disease, xanthomatosis, or other condition with a complicating metabolic disorder was present in these cases.

These patients presented (1) a characteristic clinical history of coronary thrombosis with myocardial infarction, and (2) typical, unequivocal electrocardiographic evidence of this. Each patient had been hospitalized for four to six weeks for the coronary thrombosis with myocardial infarction within a six-month period prior to the beginning of this study.

The patients who had survived the initial infarction were taken in alternate order, one patient being placed on the low-fat, low-cholesterol diet and the next on the usual, prethrombosis diet. In this way 50 consecutive patients (42 men and 8 women) with an average age of 60 years had a daily intake of 25 Gm. of fat for three years. Fifty consecutive control patients (43 men and 7 women) with an average age of 62 years adhered to the customary cholesterol-fat intake, which was judged to include from 80 to 160 Gm. of fat daily. The cholesterol content of the 25-Gm. daily fat intake was 50 to 70 mg. The daily cholesterol intake in the control series ranged from about 200 to 1,800 mg. The 50 patients on the low-fat diet had a caloric intake of a maximum of 1,500 calories, with about 320 Gm. of carbohydrate and 90 Gm. of protein.

On the diet prescribed, the vitamin A content was 9,753 I. U.; that of thiamine, 2.48 mg.; of riboflavin, 2.48 mg.; and of ascorbic acid, 140 mg.; all of which are within normal requirements. A supplementary vitamin capsule was taken orally which more than doubled the daily vitamin intake. The mineral content of the diet was also normal,

Table 1.—*Low-Fat–Low-Cholesterol Diet–Sample Menu*

		Amount	
Meal Plan		Gm.	Measure
Breakfast			
Fruit juice	Orange juice	200	6⅔ oz.
Cereal	Shredded wheat	30	1 biscuit
Skimmed milk	....	120	4 oz.
Bread	Whole-wheat toast	60	2 slices
Butter substitute	Vitamin-enriched margarine	10	1 square
Sugar	....	15	3 tsp.
Hot beverage	Coffee, tea, or substitute	......	....
Noon Meal			
Soup	Skimmed milk pea soup	150	5 oz.
Meat or cheese	Cold roast lamb, lean, with mint jelly	60 25	2 oz. 1 rounded tbsp.
Vegetables	String beans	100	¾ cup
Salad	Sliced tomato	100	1 medium
Fruit or dessert	Canned pineapple	100	1 slice
Bread	Whole wheat bread	30	1 slice
Butter substitute	Vitamin-enriched margarine	5	½ square
Hot beverage or skimmed milk	....		....
Evening Meal			
Fruit cocktail	Grapefruit	100	½ medium
Meat	Lean meats	60	2 oz.
Potato	Baked potato	150	1 medium
Vegetables	Asparagus	100	6-8 stalks
	Banana squash	100	½ cup
Salad	Fresh pear	100	1 medium
Salad dressing	Boiled dressing	20	1 tbsp.
Dessert	Lemon sherbet	90	⅛ qt.
Bread	Whole wheat bread	30	1 slice
Butter substitute	Vitamin-enriched margarine	5	½ square
Milk	Skimmed milk	120	4 oz.

FOODS PERMITTED

Soups	Bouillon or clear broths
Meats, fish poultry	All lean meat, fish, and poultry
Eggs	Egg whites as desired
Milk and milk products	Skimmed milk, low-fat cottage cheese, or buttermilk
Vegetables	All, cooked or raw
Fruits	All, cooked or raw
Salads	With vegetable oils
Cereals	All, cooked or dry
Breads	Whole wheat, rye, or rolls
Desserts	Fruits and others made without butter, eggs, or animal fats
Concentrated sweets	Jams, jellies, honey, and sugar
Beverages	Tea, coffee, and soft drinks
Vegetable oils	High in unsaturated fatty acid content: safflower, soya, corn, and cottonseed oils
Vegetable fats	Butter substitutes: vitamin-enriched margarine and soya lecithin
Miscellaneous	Nuts, olives, and avocados

FOOD PROHIBITED

Soups	Cream soups
Meats	Pork, fat meats, and animal fats
Milk and milk products	Whole milk, cream, and butter
Eggs	Egg yolks
Breads and desserts	Made with butter, whole eggs, whole milk

including about 1.009 Gm. of calcium, 1.792 Gm. of phosphorus, and 0.0222 Gm. of iron. Table 1 shows a sample menu and foods prohibited and allowed.

Results

Three Years.—The mean weight at the outset for the 42 men in the series of 50 dietetically treated patients was 166 lb. (75 kg.) and for the women, 141 lb. (64 kg.). After three years of the low-fat diet, the mean weight for men was 145 lb. (66 kg.) and for the women, 124 lb. (56 kg.). The weights of patients in the control series at the beginning and end of the three-year period were not significantly altered. Since the diet herein described is not only a low-fat but also a low-calorie diet, entailing significant weight loss in this series of dietetically treated patients, comment on the influence of the resulting weight loss in relation to their clinical disease is indicated.

Merrill[9] has recently pointed out that in treating patients with increased levels of serum cholesterol, restriction of calories should be heartily recommended to achieve optimum body weight. Reduction in weight is sometimes accompanied by a reduction in the level of serum cholesterol, particularly *if it is initially elevated*, but the amount of reduction is not determined by the degree of initial obesity.

Table 2.—*Survival Rates in Patients with Coronary Thrombosis and Infarction*

	After 3 Yr.				After 8 Yr.				After 12 Yr.			
	Death		Survival		Death		Survival		Death		Survival	
	No.	%	No.	%	No.	%	No	%	No.	%	No.	%
50 patients on normal diet	15	30	35	70	38	76	12	24	50	100	...	...
50 patients on low-fat, low-cholesterol diet	7	14	43	86	22	44	28	56	31	62	19	38

Walker and co-workers[10] found that an average weight loss of 19 lb. (8.6 kg.) in a series of 39 subjects on a low-fat, low-cholesterol diet was accompanied by a significant reduction in the level of total serum cholesterol in 21, no effect in 9, and actual increase in serum cholesterol and total lipid levels in 2 subjects. Significant cholesterol reductions tended to occur most frequently when hypercholesteremia had initially been present. The same trend and individual variability in the relationship of body weight changes to serum cholesterol levels was noted by Montoye and associates[11] as well as by me. The effects of weight reduction in the treated series of patients reported in this paper should therefore be considered, although its exact role is difficult to evaluate.

In addition to the constancy of the body weight and serum lipid levels after the three-year period of dietary treatment, adherence to the diet was checked by regular discussions of the details of the diet with the patient's spouse or a close relative living with the patient and in a position to observe the strictness of dietary adherence. No radical changes in living habits, such as exercise, were noted. There were no essential differences in medication used generally in either group of patients.

Of the 50 patients on the low-fat, low-cholesterol diet, table 2 shows that 43 were living at the end of the three-year period of observation, a mortality of 14%. Of the 50 patients on the "normal" or prethrombosis diet, 35 were living after three years, a mortality of 30%.

A breakdown of causes of death was made after the three-year period of observation. Of the dietetically treated patients, three died of recurrent coronary thrombosis with myocardial infarction, three of cardiac congestive failure, and one of pneumonia. Of the control patients, seven died of recurrent coronary thrombosis and infarction, six of cardiac congestive failure, and two of acute cerebrovascular accidents. Serum lipid and lipoprotein studies were made in these patients and are the subject of a separate communication.

Considerable reductions in all serum lipid fractions had occurred in most treated patients after the three-year period of diet therapy. The mean drop for total serum lipid levels was from 840 mg. before to 571 mg. after three years of treatment. The mean drop of neutral fatty acid levels was from 236 mg. before to 120 mg. after three years of treatment; phospholipid levels fell from 292 to 231 mg. and serum cholesterol levels from 312 to 220 mg.

The rapidity of the drop in serum lipid levels was in the order noted, i. e., total lipids were most rapid and serum cholesterol least so. An appreciable number of patients required from one to two years on the low-fat dietary regimen before a fall in serum cholesterol level was manifested. A minority of patients showed no tendency to significant decrease in serum cholesterol levels, particularly in the early phases (under one to two years) of observation.[3a] These may have respresented cases of heredofamilial cholesteremia.

The fall in total serum cholesterol levels with the corresponding fall in lipid fractions such as neutral fats requires particular comment. Some investigators[12] have noted in short-term studies that the lowering of levels of dietary fat may result in an elevation of serum triglyceride contents. Such was the case, particularly, in hospitalized patients with severe essential hypertension, especially those receiving the Kempner rice diet. These authors also found concomitant evidence of liver function impairment as measured by liver function tests in these short-term studies.

On the other hand, when decreases in serum neutral fatty acid and triglyceride levels are evaluated in response to the low-fat diet in arteriosclerotic patients uncomplicated by advanced hypertension or a rice diet, investigators such as Eggstein and Schettler[13] found in short-term studies that neutral fat and triglyceride levels fall in proportion to the drop in cholesterol and total lipid levels.

The decreases in all lipid fractions, including neutral fats, found in this series of patients on long-term diet therapy may be of particular metabolic interest, since they represent results over the longest period of study yet reported on this problem. Short-term factors of variability in lipid metabolism in arteriosclerotic patients are well known.

Eight Years.—After eight years of observation the following number of deaths occurred in both groups of patients, as noted in table 2. Of the original 50 control patients who had coronary thrombosis and myocardial infarction, only 12 were living, a survival rate of only 24%; 38 had died, mainly of cardiovascular disease. Of the original 50 patients treated with low-fat, low-cholesterol diets, 28 were living, a survival rate of 56%; 22 had died, mainly of cardiovascular disease.

The mean age for the surviving treated patients was 68 years and that for the control patients was 70 years; the age range for both groups was approximately the same, from 40 to 78 years of age. Of the 28 surviving treated patients 6 were women and 22 were men. Of the 12 surviving control patients, 4 were women and 8 were men.

Serum lipid fractions showed no significant alteration from the levels described in the discussion of three-year results of the study for the treated group of patients. Similarly, no appreciable weight changes were noted in this group.

Twelve Years.—In the control group of 50 control cases, all patients had died by the early part of the 12th year, as shown in table 2. At the same period, of the 50 patients on the low-cholesterol, low-fat diet, 19 had survived. The mortality, then, at the beginning of the 12th year was 100% for the control group and 62% for the dieting group.

As previously described, most of these patients died from recurrent forms of atherosclerosis, namely, recurrent coronary thrombosis, and a few from cerebral thrombosis or other incidental disease. Four of the 19 survivors were women, mean age 73 years, and 15 were men, mean age 70 years. The age range for both sexes among the survivors was 55 to 81 years.

No appreciable changes in weight or in serum lipid fractions were noted in the survivors, as compared with the results at the three-year and eight-year periods of observation in the same group.

Comment

Statistical evaluation of the 100 patients reported in this study is impractical because of the smallness of the sample. It would therefore be most desirable to study greater numbers of patients under controlled conditions over long periods to determine the therapeutic effects of diet, or a nutritional program of treatment, in atherosclerosis. Such a study as is now being conducted by Joliffe and his associates in the New York City Health Department with a segment of the New York City population, similar in design to this report, deserves expansion and further exploration by other investigators. The same approach which has been used for the evaluation of anticoagulant therapy in coronary thrombosis should be applied to the evaluation of nutritional or dietary treatment of coronary atherosclerosis.

In this study no differentiation was made between saturated or unsaturated fats in the diet. Emphasis was placed on the cholesterol content of the low-fat diet, thus stressing the reduction of the animal fat content of the diet. Reports on the results of unsaturated fatty acids in lowering serum lipid levels first appeared five years after the initiation of this study.

It is significant in the study of atherosclerosis that the patients observed in this report suffered from the complication of coronary atherosclerosis, namely, myocardial infarction. Possibly a different method of assessing nutritional or dietetic treatment for human atherosclerosis may be available in which the complication of myocardial infarction can be avoided. Thus, additional data may be available on therapeutic results from a nutritional approach to the treatment of atherosclerosis, the most serious health problem in America today.

Summary

A series of 100 patients with proved coronary thrombosis and myocardial infarction was observed for 12 years. Two groups of 50 patients each were studied to evaluate the results of treatment by a low-cholesterol, low-fat diet. In the control group of 50 patients who did not follow any dietary program, all patients had died by the 12th year. In the group of 50 patients treated by the 25-Gm. low-fat diet, the survival rate at the 12th year was 38%. More extensive studies of the therapeutic value of nutritional methods in the treatment of human atherosclerosis are necessary.

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HYPERNEPHROMA—FAMILIAL OCCURRENCE IN ONE FAMILY

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Three cases of hypernephroma have been found in one family. The father had died from a kidney tumor and the mother from cancer, but no autopsies were performed. Of their five children, three developed hypernephroma, the diagnoses being confirmed by biopsy in a son who died at age 52, at autopsy in a daughter who died at age 54, and at autopsy in a son who died, with the additional finding of polycythemia vera, at age 62. The disease has not been observed among members of the third generation, but none have as yet attained the above ages. The possibility that hypernephroma might have a familial tendency has not been considered in the accessible literature but is suggested by this series of cases.

In the medical literature there are many references to hypernephroma. The articles usually report a case, discuss the association of hypernephroma with polycythemia, or review a series of cases. A search of the literature failed to reveal a report that this disease can occur on a familial basis. The purpose of this paper is to present three cases of hypernephroma which occurred in one family and to speculate on the possibility of a familial tendency. Hypernephroma is also known as Grawitz tumor, renal cell adenocarcinoma, hypernephroid tumor, and clear cell carcinoma. The fact that this tumor can present different cell arrangements in different areas of the same mass leads often to confusion in its classification.

The three cases that will be presented were proved to be hypernephroma by either biopsy or autopsy. The family history revealed that the father had been treated by his family doctor for a kidney tumor; the mother died from cancer. The exact cause of deaths was not established as neither biopsies nor autopsies were performed.

Report of Cases

Case 1.—A 59-year-old man was admitted to the Allentown Hospital for the second time, Nov. 25, 1956, with a history of hematuria of two weeks duration. Earlier that year he had been admitted when he experienced attacks of pain in his chest. With each attack he had developed numbness in both arms and cyanosis of the lips and hands. The diagnosis of coronary insufficiency was made. Laboratory data demonstrated an elevated hemoglobin level of 17 Gm.% and a hematocrit value of 67%. The urine contained many red and white cells and coarsely granular casts. At that time a physical examination revealed a large liver. There had been no other illnesses. The family history revealed that the patient's mother had died of cancer, type unknown.

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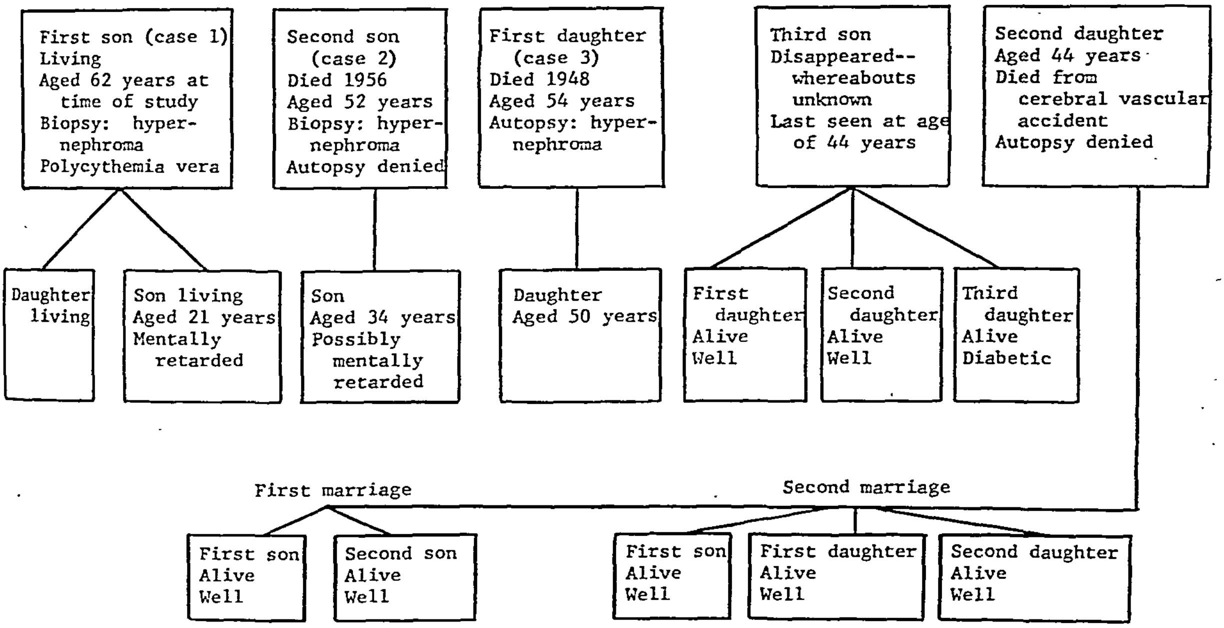
The patient was a well-developed man with a ruddy complexion. His lips were blue, and dilated veins were seen over the forehead. The skin was warm. There was a mass, considered to be the spleen, extending four fingerbreadths below the left costal margin. Moderate degree of clubbing of toes and first and second fingers of the left hand was evident. Nail beds were cyanotic. The laboratory data included a hematocrit value of 74% and hemoglobin level of 23.6 Gm.%. An intravenous urogram demonstrated change in the left kidney, indicating either tumor or cyst. Before surgery was attempted phlebotomy was done, and 2,400 cc. of blood was removed between Nov. 27 and Dec. 6. By Dec. 6 the hematocrit value had dropped to 57% and hemoglobin level was 17.5 Gm.%. Before surgery the diagnoses were polycythemia vera and renal neoplasm on the left. On Dec. 11 a left nephrectomy and adrenalectomy were performed. The kidney had been displaced anteriorly by the tumor mass, which seemed to originate from the middle portion of the kidney. Grossly it appeared to be filled with many blood vessels, which may explain the polycythemia. The pathological diagnoses were renal cell carcinoma (hypernephroma) and acute and chronic pyelonephritis. On Dec. 5, 1958, the patient was readmitted for the last time with advanced metastatic renal cell adenocarcinoma (hypernephroma). At the time of this writing the patient was being treated medically.



Descendants of man who died of kidney tumor, possibly hypernephroma.

Case 2.—A 50-year-old man was admitted to the Allentown Hospital, April 24, 1954, with a history of losing over 30 lb. (13.6 kg.) in three months time. Questioning disclosed that the patient had attacks of pain over the right iliac crest. Physical examination revealed a definite tumor-like mass over the right iliac crest, which was slightly tender to palpation. A biopsy of the right iliac crest was done on May 5. The pathological report indicated hypernephroma.

The patient had to return to the hospital once for blood transfusion and another time for incision and drainage of an abscess formation of the right iliac crest. According to the records, he was admitted to the University of Pennsylvania Hospital, Philadelphia, for a supposed chordotomy because of intractable pain. Diagnosis at that time was hypernephroma of the right kidney. The patient died March 1, 1956, after being readmitted to the Allentown Hospital for terminal care. Cause of death was hypernephroma with metastases. Autopsy was denied.

Case 3.—A 53-year-old woman was admitted for the first time to the Allentown Hospital, Jan. 1, 1947, due to complaints of abdominal pains, loss of appetite, and vomiting. Her appetite had become poor about three years before admission, and since that time she had lost over 80 lb. (36.3 kg.). Physical examination gave negative results except for a firm, nontender mass, 8 by 10 in. in the right side of the abdomen. Laboratory tests were within normal values. The patient was operated on Jan. 2. A large hard irregular retroperitoneal mass, 6 by 8 in., was removed. The pathological report stated that the mass was the shape of a kidney, 13 by 17 cm., and consisted entirely of tumor tissue which was well encapsulated. The microscopic diagnosis was hypernephroma.

The postoperative course was uneventful. The patient was readmitted several times for convulsive seizures and died Feb. 29, 1948. Autopsy was performed. Causes of death were cachexia, recurrent metastatic hypernephroma, and hypernephroma.

Comment

It was impossible at the time of this writing to draw a statistically valid conclusion from the studies of this one family (see figure). When I attempted to trace the history back into earlier generations, I was treading on uncertain ground because many of the records had been lost and memories were poor. No autopsy was obtained when the father died, and it was difficult to accurately determine the cause of his death. Of the five children, three had died of hypernephroma with metastases when they were over 50 years of age. Of the other two children, it was known that one disappeared (whereabouts unknown) at the age of 44; the other died at the age of 44 of a cerebral vascular accident, and the autopsy was denied.

When an investigation is made of a disease which appears late in life, as this one seems to, it is necessary for those being investigated to live to about the same age in order to give the highest possible incidence. At what age would the sister who did not die of hypernephroma have had to die in order to be disqualified from the inclusion in this study, and at what age would the brother have to die to be disqualified? Could I have said that these two might have developed hypernephroma if they had lived as long as the other siblings? It is my belief that it was valid to exclude from the study the two who, to the best of my knowledge, did not develop hypernephroma.

A considerable amount of work has been done in the studies of human cancer in various families. The general conclusion is that cancerous and precancerous types of lesions such as retinoblastoma, neurofibromatosis, and multiple polyposis have a definite hereditary tendency.

It is seen from the literature that most of the work in regard to the genetic nature of cancer and whether or not a particular cancer has a hereditary tendency has been done with animals such as mice. Whether or not it is valid to adapt these conclusions to the human population is questionable. One of the stumbling blocks to the study of the familial tendency for the development of cancer in humans is the inability to control the subjects that are studied. Another is in the interpretation of the study, as the family shares other things beside genes, such as their diets, habits, and sexual and social patterns. These factors must be taken into account. Before a valid conclusion can be reached in this family or any family, it is necessary to continue the study through several generations and to compare the family with a control group or to compare figures from the family with cancer with deaths expected for the population as a whole. Just because a certain type of neoplasm is concentrated *in certain families* does not necessarily prove that heredity is the casual agent. The burden is placed on the medical profession to explain why so many members of one family have the same site affected. The conclusion reached by most investigators is that there is a familial tendency *for the development of* cancer of specific organs and that cancer at other sites does not develop any more frequently than does the average comparable population. From the study of this family with hypernephroma, it can be speculated that if all the children had lived to be at least 60 years of age they would have developed hypernephroma; but would this speculation be correct?

It would be interesting to follow this family through at least another generation to see whether or not their children would have a tendency to develop hypernephroma. Before a definite conclusion can be reached, it would be necessary to do more work on this family and to study other families in which hypernephroma had appeared.

Summary

Case histories were presented of two brothers and a sister, all of whom developed hypernephroma. Observations on this family were offered as the first known demonstration that hypernephroma might exist on a familial basis.

In one of the histories there was noted the coexistence of polycythemia and renal cell carcinoma. This coexistence has been previously reported by a number of investigators, including Damon and associates.[1] Suggestion has been made to study closely the next generation.

Addendum

Since the preparation of this report the patient discussed in case 1 died. An autopsy revealed hypernephroma with metastases to the skull, ribs, vertebrae, and iliac crest.

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ANATOMICAL THEATRE.—*As soon as the Lumleian Lectures were founded, a spacious Anatomical Theatre was built, adjoining the house of Linacre, and here Harvey gave his first Course of Lectures.* $\frac{1583}{1615}$—*The Gold-Headed Cane,* London, J. Murray, 1828.

USE OF TRACHEOSTOMY IN LOWER RESPIRATORY TRACT DISEASE

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The uses of tracheostomy, which are well defined as regards upper respiratory disease, were investigated in 17 patients with such lower respiratory diseases as emphysema, pneumonitis, bronchitis, and lung abscess. Tracheostomy made it easier to assist respiration mechanically, to give oxygen, to aspirate secretions, and to administer bronchodilator drugs as aerosols. Determinations of the pH of the whole blood and the degree of oxygen saturation of the arterial blood gave objective evidence of improvement in addition to the clinical criteria. Seven patients died although many of them showed temporary benefits; nine experienced more lasting improvement, and one recovered. Two case histories illustrate the striking improvement and the definite prolongation of life occasionally obtained. The tracheostomy was usually maintained for 10 to 14 days and then removed.

The use of tracheostomy in patients with diseases other than high obstructive lesions came to the fore with its use in bulbar poliomyelitis.[1] Despite gratifying reports the procedure is less frequently used in patients with other lower respiratory tract diseases.[2] This report details our experience in 19 tracheostomies in the management of 17 patients with lower respiratory tract disease, including 12 patients with emphysema.

Methods and Materials

All patients with diseases of the lower respiratory tract who received tracheostomies under our direction during the past three years are included in this study. Wherever possible (12 patients) the clinical status of the patient was further evaluated by appropriate arterial blood gas studies. These studies included whole blood pH, oxygen saturation determinations made with either Van Slyke's and Neill's technique or a cuvette oximeter, and pCO_2 values calculated by the Henderson-Hasselbalch equation.

Patients.—Table 1 shows that 12 of the patients had emphysema, 4 had pneumonitis which in three instances was complicated by another disease, and one had bronchitis after a pneumonectomy. The patients ranged from 32 to 75 years of age. Selection was generally based on the clinical condition of the patient, although the blood gas studies made on 12 of the patients (table 2) reveal that the pCO_2 when measured was usually over 70 mm. Hg.

Mode of Treatment.—Tracheostomies were performed in the operating room whenever possible, which it was in all but two cases. The operation was performed under local anesthesia with minimal or no preoperative medication. If time permitted, a cosmetic transverse tracheostomy with incision of the third and fourth tracheal rings was performed. An endotracheal cuff was placed on the tracheostomy tube prior to insertion. As experience was gained, it was found advisable to leave the cuff inflated during the first 24 to 36 hours after tracheostomy, even when the patient was not being ventilated, to prevent aspiration of vomitus or of blood from the tracheostomy site.

Patients with labored respiration and highly negative intrathoracic pressure frequently suck air through an opened inferior pharyngeal constrictor into the esophagus, from which it passes into the stomach.[3] The dilated stomach appears more susceptible to regurgitation and the poor general condition of these patients, often including mental confusion and delayed reflexes, makes them susceptible to aspiration. The trachea and bronchial tree were thoroughly aspirated at surgery and frequently on the ward, with use of soft rubber catheters and suction pressure not exceeding 15 lb. per inch.[1b] In the unconscious patients, or in patients with heavy secretions, constant nursing was maintained by the nursing service or by carefully instructed relatives.

When necessary because of apnea or depressed respiration, ventilation was provided by the use of either an ordinary respirator or a respirator with an automatic cycling attachment. To use this equipment the endotracheal cuff was inflated and the tracheostomy tube was attached to the respirator by a polyethylene adapter and soft, flexible, corrugated rubber tubing (fig. 1).

Intermittent positive pressure breathing, in addition to its use to support depressed respiration, was used frequently (every one or two hours), with an aerosol of a bronchodilating agent, usually 0.5% isoproterenol solution. In patients with extremely tenacious secretions, continuous warmed aerosols of wetting agents such as a sterile aqueous solution

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of superinone (oxyethylated tertiary octylphenol-formaldehyde polymer) combined with glycerin and sodium bicarbonate (Alevaire) were administered through a tracheal mask. The duration of use was adjudged by the quantity and thickness of retained secretions. In all patients the atmosphere was kept moist, even if by nothing more than a wet gauze hanging loosely over the tracheostomy.

Bacteriological studies were made of the sputum and therapy begun immediately with procaine penicillin in a dosage of 600,000 units every 12 hours, unless there was a contraindication to its use. If sensitivity studies indicated a more favorable antibiotic agent, this change was made when the culture reports became available. Steroids, usually in the form of hydrocortisone sodium succinate or prednisolone, were used in 13 of the 17 patients, but their role in therapy could not be clearly evaluated.

TABLE 1.—*Data on Seventeen Patients Undergoing Tracheostomy*

Case No.	Patient Data*	Primary Diagnosis	Tracheostomy	Results	Blood Gas Studies Performed	Miscellaneous Data
1	M, 54	Emphysema	11-20-57 to 11-30-57	Improved	Yes	Therapy with steroids
2	M, 67	Emphysema	12-5-57 to 12-17-57	Improved	Yes	Therapy with steroids
3	F, 70	Pemphigus, pneumonia	1-9-58 to 1-31-58	Improved	Initially	Therapy with steroids and nebulization
4	M, 68	Emphysema	1-30-58 to 2-8-58	Improved	Yes	Therapy with steroids and nebulization
5	M, 58	Pneumonitis, atelectasis, emphysema	1-29-58 to 12-3-58	Improved	Yes	Therapy with steroids and nebulization
6	M, 76	Emphysema	1-30-58 to 2-2-58	Died	Yes	Therapy with steroids; uremia; digitalis intoxication
7	M, 70	Emphysema	2-2-58 to 3-6-58 and 4-11-58 to 6-29-58	Improved Died	Yes Yes	Therapy with steroids and nebulization
8	M, 52	Emphysema	8-15-57	Died	Yes	Therapy with steroids
9	F, 44	Postpneumonectomy, indefinite bronchitis	11-22-57 to 11-27-57	Improved	No	Therapy with steroids
10	M, 32	Postpoliomyelitis, bronchitis, pneumonia	3-7-58 to 3-20-58	Improved	Yes	
11	M, 55	Asthma, emphysema, bronchitis	3-20-58 to 4-7-58	Improved	Yes	Therapy with ACTH and nebulization
12	M, 42	Pneumonia	2-11-58 to 2-23-58	Recovered	No	White blood cell count 2,150 per cu. mm.; therapy with steroids and nebulization
13	M, 63	Emphysema, lung abscess	9-26-58 to 9-30-58	Died	No	Therapy with nebulization
14	M, 74	Emphysema, pneumonitis, diskitis	11-4-58 to 11-16-58	Improved	Yes	Therapy with nebulization
15	M, 75	Pneumonia, heart failure	3-23-57 to 3-25-57	Died	No	Nonprotein nitrogen level, 150 mg. %
16	M, 44	Emphysema, lung abscess (staphylococcic)	1-17-59	Died	No	Therapy with steroids
17	M, 62	Emphysema	1-18-59 to 1-19-59	Died	No	Morphine poisoning

* Sex and age, yr.

Results

Of the 17 patients 7 ultimately died, even though many experienced initial benefit. One of the deaths followed a third hospital admission and a second tracheostomy (case 7). Another death occurred from multiple staphylococcic lung abscesses about two months after the tracheostomy was done (case 16). When the patients are grouped according to their presenting symptoms it is noted that there were only three deaths in nine tracheostomies on seven noncomatose patients (fig. 2). One death was due to aspiration of vomitus that occurred while the cuff on the tracheostomy tube was not inflated (case 7).

In the group of patients who were semicomatose or comatose at the time of tracheostomy (fig. 3), the death rate was much higher. It must be pointed out that two of the deaths were associated with the injudicious use of narcotics, and two patients were not treated in a manner that we would presently

TABLE 2.—*Findings of Blood Gas Studies*

	Before Tracheostomy						After Tracheostomy			
Patient	pH	O_2 Saturation, %	pCO_2	Hematocrit Reading	Days Before	Days After	pH	O_2 Saturation, %	pCO_2	Hematocrit Reading
7 (1st tracheostomy)	7.20	83.5	96	50.5	Same day	10	7.29	86.2	65	47
7 (2nd tracheostomy)	7.37	71.5	70	49.0	...	22	7.40	82.1	63	49
4	7.38	63.0*	77	55.0	1	7	7.39	81.0	57	...
11	7.46	87.1	67	46.5	1 after	9	7.43	85.8	46	44
18	7.35	86.0*	85	...	Same day	18	7.38	91.4	49	39
10	7.39	77.2	60	44.0	1	4	7.37	88.0	55	35
8	6.98	...	120	61.0	1	Same day	7.14	...	105	...
2	7.34	51.8	76	49.5	1	7	7.39	81.3	57	49
	7.25	36.0*	95	47.4	Same day					
13	7.19	68.8	66	42.0	Same day	...	...	...	...	...
6	...	...	...	...	...	2	7.12	77.0*	54	...
19	7.34	67.0*	51	34.0	...	...	...	...	...	...
14	...	...	...	...	...	4	...	86.5	58†	...

* Oximeter reading.
† CO_2 content, volume %.

consider to be adequate. Of the 17 patients, 12 had emphysema and among these were six of the seven who died.

Report of Illustrative Cases

Case 5.—A 57-year-old man was admitted to the surgical service because of an undiagnosed infiltrate in the left lung. Shortly after admission he became severely dyspneic and was inadvertently treated with meperidine, which further depressed his respiration. Arterial blood gas studies made shortly thereafter showed a pH of 7.36, a pCO_2 of 85 mm. Hg, and an oxygen saturation of 86%. A tracheostomy was performed immediately and vigorous therapy was begun with suction, isoproterenol administered by aerosol, administration of antibiotics, and intermittent positive pressure. Two days later his pH was still 7.36, pCO_2 78 mm. Hg, and oxygen saturation 81% (although this oxygen saturation determination was made with the patient breathing room air rather than oxygen, as during the previous determinations). Eighteen days after the tracheostomy his pH was 7.38, pCO_2 49 mm. Hg, and oxygen saturation 91%. The tracheostomy was maintained, since attempts at removal resulted in recurrence of respiratory failure from his chronic emphysema. In the ensuing six weeks roentgenograms of his chest showed clearance, but still it was not possible to remove the tracheostomy tube. He was discharged only to be admitted on five subsequent occasions in acute respiratory failure due to respiratory infections, which all responded to vigorous therapy. Only about 10 months later did it become possible for him to tolerate closure of the tracheostomy.

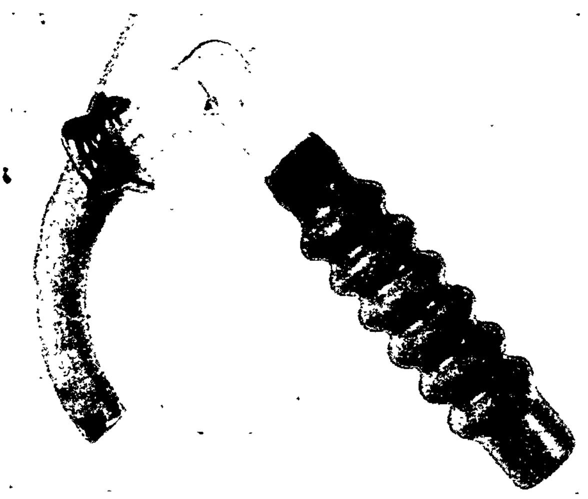

Fig. 1.—Tracheostomy tube, with endotracheal tube cuff and plastic adapter to attach to tubing of respirator.

Comment.—This case illustrates the clearing of a pulmonary infection and the improvement in respiratory function that can follow adequate tracheal cleansing. At this time, whenever it becomes necessary for a tracheostomy to be maintained on a permanent basis, we prefer to switch to fenestration tracheostomy, as developed by Rockey[4] and co-workers. This type of tracheostomy has the advantage of being available for intubation whenever necessary but closed at other times to allow normal breathing, talking, and coughing.

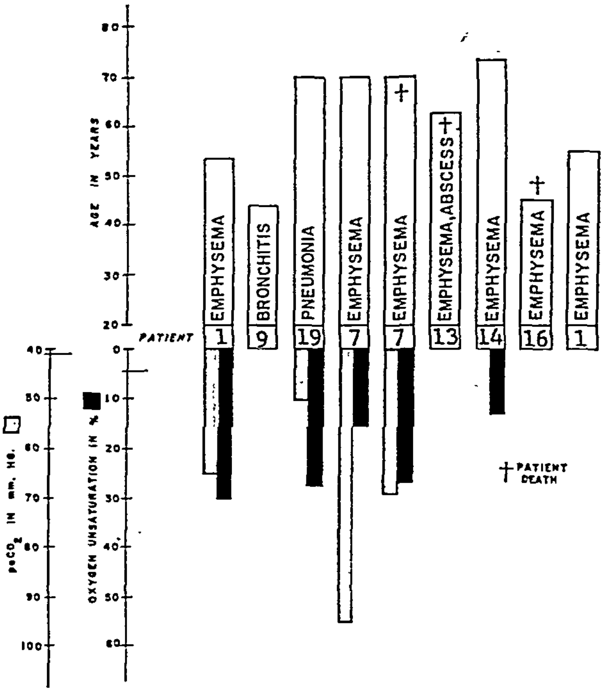

Fig. 2.—Graph showing ages, diagnoses, blood gas values, and fates of dyspneic patients.

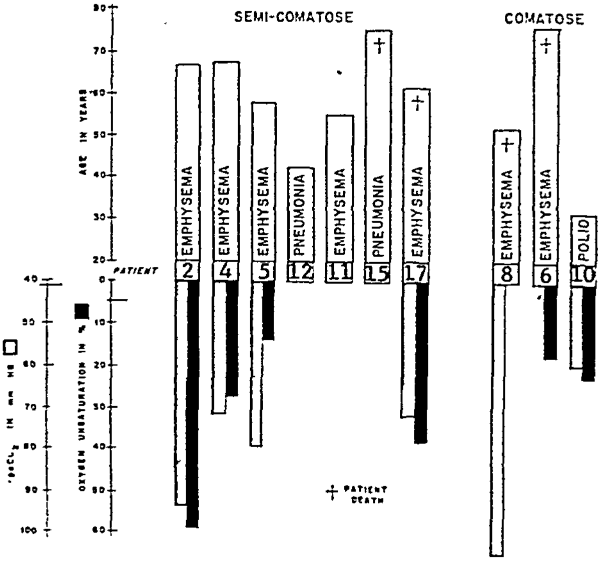

Fig. 3.—Graph showing ages, diagnoses, blood gas values, and fates of comatose and semicomatose patients.

Case 7.—A 69-year-old man was seen three months before admission with findings of severe respiratory failure due to emphysema, with an oxygen saturation of 90% and a pCO_2 of 59 mm. Hg. On admission his pH was 7.20, $paCO_2$ 85 mm. Hg, and oxygen saturation 73%. One day later his pH was 7.20, pCO_2 96 mm. Hg, and oxygen saturation 83%, even though he was receiving oxygen. A tracheostomy was done that evening and the following day his pH was 7.29, pCO_2 72 mm. Hg, and oxygen saturation 74%. Studies two days later revealed a pH of 7.37, pCO_2 of 62 mm. Hg, and oxygen saturation of 77%. Eleven days after the tracheostomy his pH was down to 7.29 again, his pCO_2 at 65 mm. Hg, and his oxygen saturation up to 86%. Because the patient had made a good clinical recovery, the tracheostomy tube was removed that day.

The patient had to be readmitted one month later for the same complaints, and blood gas studies at that time revealed a pH of 7.37, a pCO_2 of 70 mm. Hg, and an oxygen saturation of 72%. It was necessary to repeat the tracheostomy, and it was decided to maintain the tracheostomy indefinitely. He was readmitted again three months later, because of respiratory failure from another acute infection. He made an excellent immediate response to therapy, but on his second day after admission, in the presence of a resident, he vomited while eating, aspirated his vomit, and died instantly (fig. 4).

Comment.—This patient had been extensively studied and his life was definitely prolonged by tracheostomy. As in most patients with pulmonary insufficiency and infections, the blood gas values did not return to normal until the infection was well under control. The almost instantaneous death after aspiration noted in this case apparently was due not to suffocation but to cardiac arrest. One other patient had a dangerous episode of vomiting which, fortunately, did not prove fatal.

Comment

This method of treatment has proved useful in the treatment of severely ill patients who have had an exacerbation of a chronic pulmonary disability and in patients with overwhelming pulmonary disability due to an acute complication. It is most useful whenever retained secretions play a prominent role, as in acute bronchitis in a patient with emphysema. This plan of treatment requires meticulous attention to details and vigorous nursing care on the part of the nursing staff and the physician involved.

Comparison of these data with the work of other authors[5] is somewhat difficult because of the small size of some of the series and the marked differences in the severity of illness. Sieker and Hickam[6] reported 13 survivals in 25 patients treated with a tank respirator and endotracheal intubation. Their data suggest that their patients were more seriously ill, but they mentioned difficulties in overcoming the patients' own respiratory cycles with the respirator, a complication avoided by this method of treatment. Westlake, Simpson, and Kaye[7] reported 14 survivals in 16 patients with carbon dioxide narcosis of short duration and much less severity effected with use of an oxygen tent intermittently or oxygen by nasal catheter at low flow rates.

Regardless of the mode of ventilatory assistance selected—even if only a rebreathing bag and mask—any patient with severe hypoxia, whatever the other existing circumstances, must be given oxygen. The presence of hypercapnia and hypoxia, with the latter acting as the only significant respirator stimulus, means that the patient needs oxygen plu ventilatory assistance, not that oxygen is contra indicated. This point cannot be too strongly em phasized, in view of the long-standing and preva lent misconception that oxygen is contraindicate

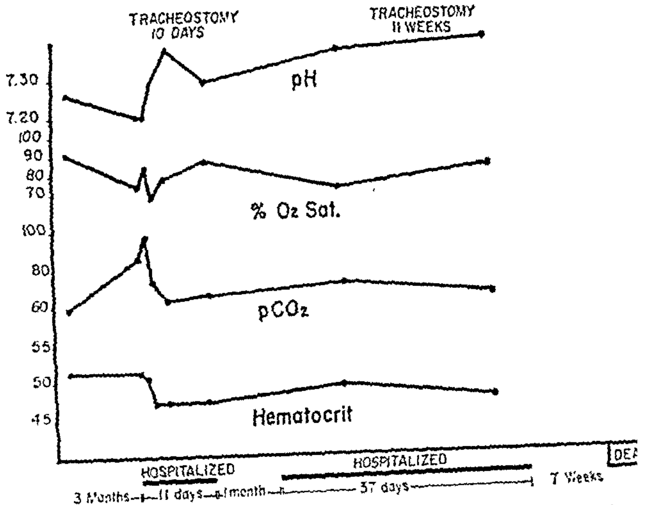

Fig. 4.—Graph showing clinical course and blood values of patient 7.

in such circumstances. This pernicious practice h undoubtedly contributed to the death of ma respiratory cripples, just as may the use of oxyg without ventilatory assistance, when both are in cated. Since only a mask and rebreathing bag, su as are available on any anesthesia machine, required for this therapy there is no excuse for correct or partial therapy.

The mechanism of the favorable response tracheostomy is probably a combination of fact Those that may be involved are a reduction in de space of 100 to 150 ml.,[8] a decrease in airway sistance through by-passing the larynx, and an crease in the ease of removal of secretions. latter may be most important, since patients having significant secretions received less ben from the tracheostomies. The procedure does replace any destroyed tissue but will allow ai reach alveoli which are still functional.

The tracheostomy was usually maintained 1 14 days and then removed. This observation sh help to remove a part of the stigma attached, even by physicians,[9] to this lifesaving procedure. In only two of our patients have we thought a permanent tracheostomy—fenestration or otherwise—to be indicated.

Summary

Treatment with tracheostomies for diseases of the lower respiratory tract is of most value in patients with retained secretions, regardless of the cause, but it cannot restore destroyed lungs. In 17 patients, with 19 tracheostomies, 14 were benefited by the procedure, although only 11 ultimately survived. The mechanism of improvement is thought to be a reduction in dead space, a decrease in airway resistance, and an improvement in bronchial toilet. Anoxia, as well as hypercapnia, should be corrected immediately in all such patients by the use of assisted respirations whenever required.

2500 N. State St. (Dr. Webb).

This study was aided in part by a grant from the National Institutes of Health.

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BURKING.—The men engaged in the business of supplying the dissecting rooms were generally referred to by the medical students as "Sac 'emup men." The name was derived from the fact that the bodies were conveyed through the streets and delivered to the school enclosed in heavy, strong sacks. If the bearers were overtaken in transit by an officer of the law, they were quickly allowed to go scot-free—officers did not like to have on their hands such a frightening catch. This unholy traffic came suddenly to an end a few years later, as a result of a terrific scandal which grew out of it. In Edinburgh a man named Hare murdered a tenant who owed him a small sum, and then secretly offered the body for sale to the anatomical department of the Edinburgh University. No questions were asked except about the price, which proved to be an amount well over the debt the dead man owed him. This gave the depraved villain an idea of how huge profits might be easily gained. He took in partnership a man named Burke, who made it his business to lure unsuspecting victims to an inn; once there, they were plied with alcohol to the point of insensibility, and then suffocated. This nefarious practice was conducted successfully for some time, due to the fact that the method of murdering, afterwards spoken of as "Burking," left no telltale evidence of violence. When at last they were caught up with, the shock produced by the disclosure had the effect of getting a new Parliamentary law passed; by making reasonabe provision for the medical school, it put an end to the business of body-snatching and provided for the needs of the science of anatomy—thus correcting two evils at the same time.—W. A. Wells, A Doctor's Life of John Keats, Vantage Press, New York, 1959, page 93.

J.A.M.A., June 25, 1960

CLINICAL NOTES

METASTASIS FROM HYPERNEPHROMA TWENTY YEARS AFTER NEPHRECTOMY

REPORT OF A CASE

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and
Richard Rubin, M.D., Brooklyn

Although there has been mention in the literature of the past 30 years of long-term survival of patients with renal cell carcinoma, case reports of patients who have survived for 20 years with this disease are rare.[1] In a study by Deming,[2] it was found that 19.5% of patients with cases of proved hypernephroma were alive at the end of 5 years and 14.6% were living at the end of 10 years; only 9.08% were free from tumor at the end of the 10-year period. Of the various histological forms, patients who have renal cell carcinoma growing in solid cords with isometric components and heavy trabeculae have the best prognosis.[3]

A 63-year-old woman was admitted for the second time to the Maimonides Hospital. Her chief complaints were generalized weakness, weight loss of 15 lb. (6.8 kg.), chest pain, and a nonproductive cough of two to three months duration. The patient denied any symptoms referable to the urinary tract. Twenty years before the patient had been admitted to this hospital and a nephrectomy had been performed on the right for a renal cell carcinoma (fig. 1). After surgery, the patient received radiation therapy at the operative site. In the interim she remained asymptomatic, and frequent observations in various clinics failed to reveal any evidence of recurrence.

At the time of admission physical examination revealed a well-developed, well-nourished, elderly woman in no apparent distress. Her vital signs were as follows: blood pressure, 110/70 mm. Hg; pulse rate, 88 regular beats per minute; respirations, 20 per minute; and temperature, 98 F (36.7 C). The remainder of the physical examination showed unremarkable findings. Laboratory studies revealed the following information: hemoglobin level, 14.8 Gm.%; red blood cell count, 4,700,000 per cubic millimeter, white blood cell count, 9,100 per cubic millimeter; hematocrit value, 47 vol.%; and sedimentation rate, 40 mm. per hour (corrected, Wintrobe). Urinalysis revealed an alkaline urine with a specific gravity of 1.006 and no protein, sugar, or acetone; microscopic study showed negative findings. Her fasting blood-sugar level was 88 mg.%, blood urea nitrogen level 18 mg.%, and uric acid level 4.2 mg.%. The phenolsulfonphthalien excretion value was 43% in two hours. The specific gravity of the most concentrated urine specimen studied in a Fishberg test was 1.007. The urea clearance was 33 ml. of plasma per minute, which is 61% of normal. The total protein level was 6.9 Gm.%, and the albumin-globulin (A/G) ratio was 3.6/3.3.

X-Ray examination of the chest revealed two large secondary deposits in the right and left lung (fig. 2). Bone survey revealed an osteolytic lesion on the medial and posterior aspects of the lower shaft of the left femur (fig. 3). Examination of the left shoulder showed an osteolytic destructive process involving the supraspinatus portion of the scapula and extending to the acromial insertion. Intravenous pyelography revealed a normal left kidney and absence of the right kidney.

A biopsy of the femoral lesion was performed, and this revealed marked bone replacement by tumor formed of irregular acini and masses of polyhedral clear cells having small nuclei. The histological diagnosis was metastatic clear cell carcinoma (fig. 4). This picture was identical to that seen on the original slide 20 years ago.

During her hospital stay, the patient received supportive therapy and radiotherapy to the chest, scapula, and femur consisting of a total of 2,100 r in air to the lungs, 2,250 r in air to the scapula, and 1,100 r in air to the left femur. She was then discharged and sent to a nursing home.

Comment

Renal carcinoma may have a prolonged and, at times, bizarre course. It has been found that renal carcinoma most commonly metastasizes to bone, brain, and lung, and sometimes to skin, gallbladder, bile ducts, corpus cavernosum, epididymus, intestine, pancreas, thyroid gland, pericardium, heart, mediastinum, seminal vesicles, mouth, external auditory meatus, and phalanges.[4] In a study of 195 patients with hypernephroma at the time of first admission,[4a] 37% were found to have metastasis. Most cases occurred in the lung (34 cases, 48%) and bones (16 cases, 23%). Of the cases of metastasis of

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the bones, six occurred in the spine, three in the humerus, three in the pelvis, two in the skull, one in the femur, and one in the scapula. In a study of 1,458 cases, Abeshouse and Goldstein found that 26.5% of renal tumors metastasized to the opposite kidney. This confirmed a previous statement by Young[5] that metastatic renal tumors are most commonly associated with primary renal neoplasm. Metastasis from renal neoplasm may occur in only one organ. Those in the lung may occur as single nodules or cotton wool patches. Skeletal metastasis often involves the ends of long bones, and pathological fractures are common and are often the first sign of the malignancy. Here there would be areas of cortical or spongy bone destruction with no periosteal reaction or new bone formation.[4c]

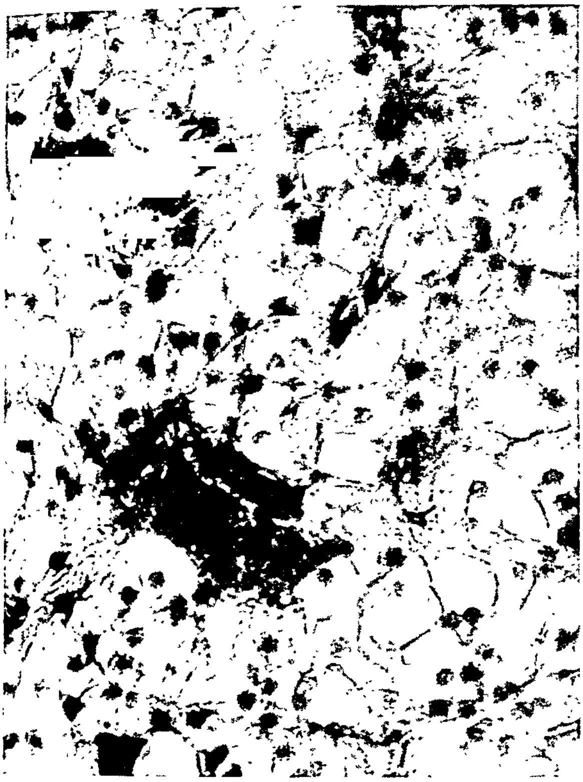

Fig. 1.—Renal cell carcinoma of right kidney.

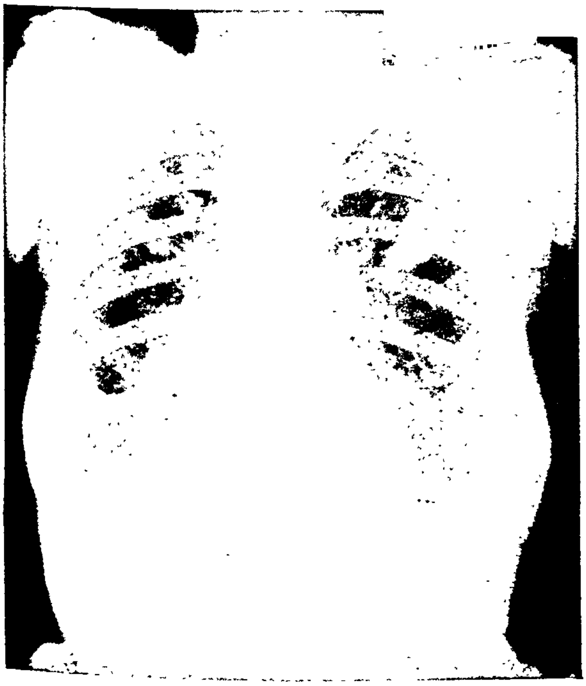

Fig. 2.—Posteroanterior view of chest.

In our patient, no evidence of metastatic disease was present until 20 years after the initial diagnoses. At this time metastasis to the lung, femur, and scapula was observed. As far as could be ascertained, the left kidney was free of metastatic disease. In a review of the literature only a few instances of 20-year survival were encountered.

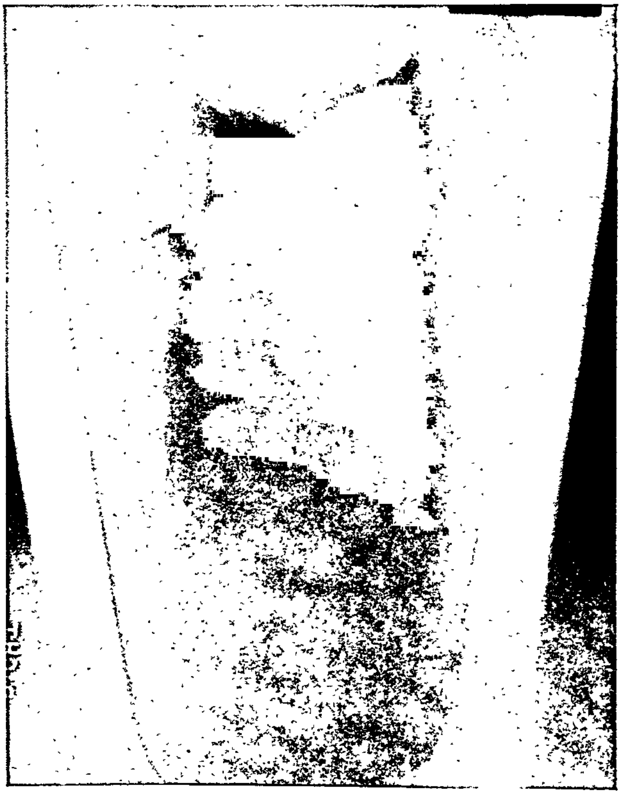

Fig. 3.—Lower shaft of left femur.

Graves and Mabrey[1a] recorded a recurrence in the scar and lumbar area 20 years after the removal of the original kidney adenocarcinoma. Starr and Miller[1b] removed a solitary jejunal metastasis 20 years after nephrectomy for a clear cell carcinoma, and Sabdine[1c] noted calcified cystic carcinoma developing after 20 years. A 19-year survival of a patient who had carcinoma of the kidney was reported by Estragant and Durand.[1d] In a survey of long-term survivals in patients with various types of carcinoma, Morton and Morton[6] reported a case of hypernephroma which metastasized to the right femur and manifested itself 16 years after kidney removal for the original lesion. This was treated by disarticulation and roentgen therapy (4100 r in air) after which the patient was free from disease after 8 years of follow-up examinations (total of 24 years).

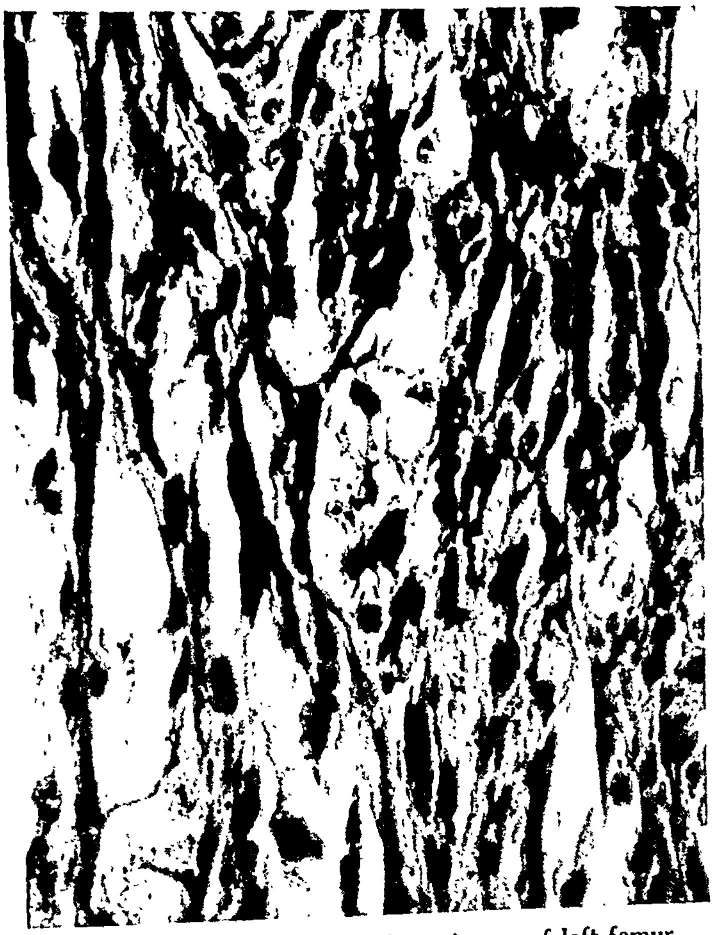

Fig. 4.–Metastatic clear cell carcinoma of left femur.

Recurrence of carcinoma many years after resection of the primary lesion is a manifestation most commonly seen in carcinoma of the thyroid and occasionally in carcinoma of the breast, in ocular and cutaneous melanoma, and in hypernephroma.

Summary and Conclusions

A brief review of the literature has indicated that 20-year survivals after the diagnosis of renal cell carcinoma are rare. Prompt therapy followed by close supervision, however, can be rewarding.

Addendum

The patient in this study died several months after having been sent to a nursing home. Permission for postmortem examination was not obtained.

U. S. Army Dispensary, Concourse, The Pentagon, Washington, D. C. (25) (Dr. Rosof).

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TREATMENT OF PSORIASIS WITH INTRALESIONAL INJECTIONS OF TRIAMCINOLONE

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and
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The effectiveness of orally administered triamcinolone in 60% of the cases treated was first reported by Shelley and colleagues[1] in a series of 60 patients with psoriasis. Of 21 of these patients who had skin tests in a psoriatic lesion with a 1% suspension of triamcinolone, 11 showed a zone of clearing at the injection site. Subsequently one of us (R. L. B.) with Cohen[2] demonstrated that triamcinolone in suspension injected intradermally produced larger zones of clearing in psoriatic plaques than other cortisone analogues similarly given. In view of these results, treatment of persistent plaques of psoriasis with locally injected triamcinolone was undertaken.

Materials and Methods

Because of the technical difficulty of injecting large plaques intradermally, the suspension of 1% of triamcinolone acetonide or of 2½% of triamcinolone diacetate was given subcutaneously, attempting however, to inject as superficially as possible. Either a 23-gauge 1.5-in. needle or a 26-gauge 1-in. needle was used, a technique which permitted

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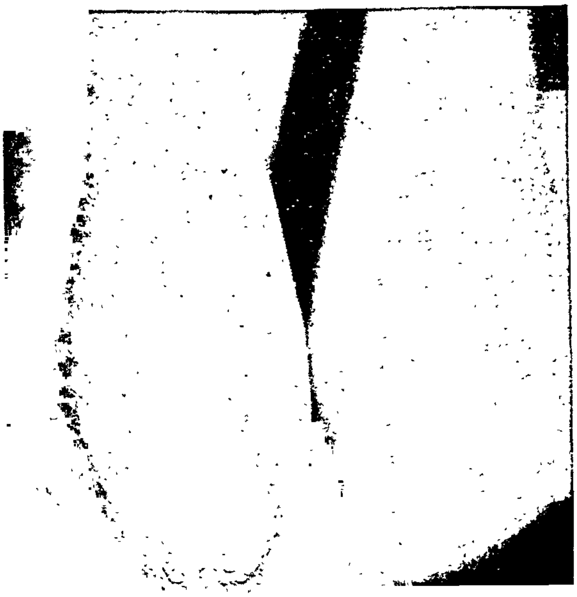
Treatment of Patients with Psoriasis with Locally Injected Triamcinolone

Case No.	Sex	Age	Eruption, Duration	Previous Therapy	Sites Injected	Approximate Size of Lesion, Cm.	Injections No.	Response	Comment
1	F	30	3 mo.	Topical	Dorsum of hand; eyebrow	3 3	1 1	Clear in 3 wk.	No recurrence in 6 mo.; new lesions at other sites.
2	F	29	5 yr.	Topical for 1 yr.	Elbow	5	1	Clear in 10 days, except 2 0.5 cm. areas at periphery	No recurrence in 4 mo.; 2 small lesions injected—cleared in 2 wk.
3	F	47	10 mo.	X-ray; topical	Pretibial	9 by 8	1	Clear in 3 wk.	No recurrence in 4 mo.
4	F	55	1 yr.	None	Pretibial; thighs; buttocks	3 by 2	1	Clear in 2 wk.	
5	F	69	8 yr.	X-ray; topical	Palm; wrist	6 1	1 1	16 F 25 mo.	No recurrence in 3 mo.
6	M	42	20 yr.	X-ray; topical	Elbow	4	1	80% clear in 1 wk.	No follow-up
7	F	25	20 yr.	X-ray	Forearm; thumb; palm	Total 5	1 1	Clear in 4 wk., except erythema in 1 patch	
8	M	57	2 mo.	None	Knees; trunk	5 by 3	2	No response	No response to orally given triamcinolone 16 mg. daily
9	M	28	2 yr.	Topical	Intergluteal	8 by 2	1	Clear in 2 wk.	No recurrence in 3 mo.
10	F	30	7 yr.	X-ray	Elbow; ankles	8 by 5 2	2 1	One patch clear, 2 patches 90% clear in 3-6 wk.	Abscess left forearm 3 wk. after injection; slight depression remains in ankle area
11	M	48	4 yr.	None	Elbows; knuckle	6 1	1 1	Only erythema after 12 days	
12	F	39	3 mo.	Grenz rays	Elbow; forearm; hand	11 by 6 2 by 1 1 by 1	1 1 1	Clear in 2-3 wk.	Site injected clear 8 wk. later, with flare at periphery and on contralateral hand
13	F	33	2 yr.	Topical	Elbow	3	1	Clear in 2 wk.	Half of lesion not injected; no change there
14	F	58	14 yr.	Topical; grenz rays; thorium X	Palm	6 by 6 4 by 4	2	Clear in 4 wk.	No recurrence in 6 mo.
15	M	31	2 yr.	Topical; grenz rays	Dorsums of hands	2 by 2	4	Clear in 8 wk.	Slight depression of injected sites; no recurrence in 6 mo.
16	F	25	*	Topically and orally given triamcinolone	Leg	1	1	Clear in 3 wk.	
17	F	38	5 yr.	X-rays; topically and orally given triamcinolone	Elbows	5 by 3	1	Clear in 3 wk.	2 guttate lesions recurred in 6 mo. in center of site
18	M	7	10 mo.	Topical	Tibia	4 by 3	1	Clear in 3 wk.	
19	F	52	7 mo.	Grenz rays; topical	Scalp	3 by 3	1	Clear	Slight depression lasting several mo. associated with partial alopecia
20	F	55	13 mo.	Grenz rays; topical	Elbow	2 by 2	1	Cleared 90% in 1 wk.	Small areas of recurrence after 3 mo.

* Several months.

treatment of large lesions with relatively few skin punctures. The suspension itself caused little or no pain when instilled. Puffiness of the injected areas, lasting for a few hours, was observed in some instances. In our series of patients, the largest dose of triamcinolone used for one site at one time was 4 cc. injected into a plaque measuring 11 by 6 cm. through multiple punctures along the periphery of the lesion. Smaller lesions were injected through one puncture site. All other therapy was discontinued while the corticosteroid injections were used.



Photograph made two weeks after injection of suspension of 1% of triamcinolone acetonide into lesion on left forearm of patient in case 12.

Results

Within one week after treatment, areas of normal skin scattered throughout the injected plaque appeared in most patients, and scaling and erythema in the rest of the lesion were much reduced. Within another week or two many lesions had cleared (see the figure). The effect of this treatment was entirely local, since none of the lesions at noninjected sites near or distant to the treated areas showed any improvement. No systemic side-effects were noted. However, when administration of large quantities of triamcinolone in suspension is required, it may be advisable to inject the plaque, or plaques, piecemeal on different days.

The details of the results are reported in the accompanying chart. Of the 20 patients treated, only 1 did not clear or show distinct improvement. It is interesting to note that this patient also did not respond to orally administered triamcinolone.

In one patient the site injected eight weeks previously was observed to remain clear although the psoriatic eruption continued to spread on both hands. Three patients developed mild depression at the sites treated, and one of these also developed an abscess three weeks after infiltration of a site on the forearm.

In two of the cases which have cleared, there has been a recurrence of psoriasis at a treated site three and six months, respectively, after treatment. The longest follow-up has been seven months.

Summary

The subcutaneous injection of 1% of triamcinolone acetonide in suspension or of 2½% of triamcinolone diacetate in suspension into persistent psoriatic plaques was effective in clearing or markedly improving the lesions in 19 of 20 cases. The side-effects were slight depression at the injected sites in three patients and abscess formation in one. This procedure constitutes a simple, effective, and rapid method of treating localized, persistent lesions psoriasis.

962 Park Ave. (28) (Dr. Baer).

Cases 19 and 20 (listed in chart) were treated by I Marion B. Sulzberger, Victor H. Witten, and Alfred Kopf.

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Note: Since this paper was written the following arti has been published: Gerard, A. G.: *Treatment of Psori with Subdermal Infiltration* of Triamcinolone Diacetate S pension, A. M. A. *Arch. Dermat.* **81**:535-538 (April) 19

RUPTURED PEPTIC ULCER DURING TRIAMCINOLONE THERAPY

REPORT OF A CASE

Abraham W. Danish, M.D.
and
Manuel P. Landman, M.D., Washington, D. C.

This is believed to be the first reported case of ruptured peptic ulcer resulting from triamcinolone (Aristocort) therapy.

A 76-year-old man was brought to the office of one of us (M. P. L.) on Nov. 10, 1958, with a severe case of pemphigus vulgaris of five weeks' duration. Bullae involved 80% of the body and varied in size up to 10 cm. One-third of the body was denuded where bullae had ruptured, and weeping of a foul-smelling material was present in the area. Mucous membranes were involved to the extent that food and fluid intake was severely restricted because of pain. The anal area was similarly involved. Immediate hospitalization was advised.

The patient was admitted to Suburban Hospital, Bethesda, Md., on the same day. Laboratory studies revealed hemoglobin level, 11 Gm. per 100 cc.; hematocrit value, 37 vol.%; sedimentation rate (Wintrobe), 50 mm., corrected to 32 mm. per hour; leukocyte count, 10,000 per cubic millimeter, with segmented forms 62%, staff cells 13%, lymphocytes 16%, monocytes 8%, and eosinophils 1%. Urinalysis showed negative results.

Therapy with 24 mg. of triamcinolone per day and 30 units of ACTH per day, as well as vitamins and local therapy, was started on admission of tl patient. Within two days a marked improveme had occurred. By the fourth day the weeping ha almost stopped, many bullae were absorbed, an few new ones appeared. Triamcinolone dosage w reduced to 16 mg. daily, and 20 to 30 units ACTH was administered every two to four days.

The course was uneventful until the 17th hospit day (Nov. 27), when the patient complained c headache and several hard, sensitive areas appeared on the scalp. These increased in size an number and developed into furuncles. Dosage o triamcinolone was reduced to 12 mg. daily. Although the pemphigus seemed to be well controlled, the furunculosis spread over the scalp an nuchal area and the patient's general conditio deteriorated. On Nov. 30 a slight fever was noted the patient was lethargic, and the pulse rate wa rapid and irregular. Therapy with tetracycline, 25 mg. four times daily, was started.

On the evening of Dec. 2 (22nd hospital day) one of us (A. W. D.) was called to see the patient because of the nondermatological aspects of the case. In addition to the skin infection, the patient was now complaining of diffuse abdominal pain which had started that evening. The pain could not be adequately described but seemed not to be severe. There were many eructations, and the tongue was

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Associate in Medicine (Dr. Danish) and Clinical Instructor in Dermatology (Dr. Landman), George Washington University School of Medicine.

dry. The lungs were clear. There was tachycardia with gross irregularity of the heartbeat. The abdomen was soft with little tenderness and no rebound; peristalsis was diminished but not absent. Results of the rectal examination were negative, and the stool on the examining finger was light brown. At the time an electrocardiogram showed supraventricular tachycardia with occasional premature ventricular beats and bouts of auricular fibrillation. Urinalysis revealed a specific gravity of 1.015; a trace of albumin; sugar 3+; and few leukocytes. The hemoglobin level was 12.6 Gm. per 100 cc.; hematocrit value 43 vol.%; sedimentation rate 43 mm., corrected to 36 mm. per hour; and leukocyte count 20,350, with segmented forms 61%, staff cells 30%, lymphocytes 5%, and monocytes 4%. The blood urea nitrogen level was 20 mg. per 100 cc. and glucose level 275 mg. per 100 cc. Fluids were given intravenously, and 25 units of regular insulin was given. Later that evening the blood sugar level was 232 mg. per 100 cc. The next morning, the fasting blood sugar level was reported as 35 mg. per 100 cc. The patient ate and retained a full breakfast. He was disoriented at times, his pulse rate and respiration rate were rapid, and his rectal temperature was 103 F (39.4 C). Shortly thereafter the patient suddenly died.

The total dose during the 23 days of hospitalization was 364 mg. of triamcinolone and 220 units of ACTH. Other medicaments given included methylparofynol (Dormison), aspirin compound with codeine (Empirin), and meperidine (Demerol) hydrochloride.

Autopsy was performed the same day by Dr. Edward G. McGary. Positive findings were as follows. The skin of the body was covered, over the neck, thorax, extremities, and back, by violaceous, elevated lesions and by violaceous lesions whose superficial surface had been denuded and appeared slightly ulcerated. On the left shoulder some of these lesions contained a creamy, purulent material. The violaceous area was bordered by a narrow perimeter of erythema. The lesions were markedly indurated where they were elevated above the skin surface. Elsewhere there were blue-red discolorations which formed no distinctive pattern. The peritoneal cavity, opened under water-seal drainage, revealed the presence of gas to pressure. There was 1,500 cc. of turbid, cloudy, light brown fluid present in the peritoneal cavity, and there was a fibrinous exudate covering the loops of the intestines.

Separation of the transverse colon from the liver and gallbladder revealed, in situ, a perforation of the first position of the duodenum. The diameter of the perforation was 1.2 cm. Food particles and gastric and duodenal juices were seen exuding from this perforation. The right lung weighed 460 Gm., the left lung 340 Gm. They were deeper red in color than usual. There was a partially attached antemortem thrombus in the primary branch of the pulmonary artery to the right lung which extended primarily into the branches to the lower lobe of the right lung. The parenchyma of both lungs were moderately congested. The heart showed some tigroid streaking of the myocardium and a moderate degree of calcification of the mitral and aortic valve rings. There was an area of ulceration and perforation 2.5 cm. distal to the pylorus on the right lateral duodenal wall. The liver revealed a slight degree of congestion. The pathological diagnosis was pulmonary embolism, perforated duodenal ulcer with generalized peritonitis, pemphigus vulgaris, and secondary staphylococcic infections of the skin.

Comment

Peptic ulceration, either gastric or duodenal, is a complication to be considered in anyone receiving steroid therapy. Symptoms may be typical and severe so that treatment is required, or an ulcer may be demonstrated by x-ray even in the absence of symptoms.[1] At times the first symptoms may be the onset of a complication such as hemorrhage or perforation. The latter may be difficult or impossible to detect due to the masking action of the steroid, as in the patient who has been discussed in this report. The possibility of ulcer perforation must be considered in anyone receiving steroid therapy so that symptoms may be investigated quickly and therapy instituted without delay.

Hilbish and Black [2] reported an interesting case of presumed perforation of an ulcer occurring in a man taking prednisone; routine chest x-ray showed free air under the diaphragm, although the man had no symptoms of perforation. The patient responded well to medical therapy, and the perforation was, therefore, not confirmed by operation or autopsy. Ulceration may occur at any time during the course of treatment, as early as two weeks or as late as after several years of therapy. Brown and Haserick [3] reported three cases of peptic ulcer in patients taking triamcinolone. Symptoms occurred three to six weeks after starting the use of the new medicament or changing to triamcinolone from some other steroid.

927 Pershing Dr., Silver Springs, Md. (Dr. Danish).

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PULMONARY HISTOPLASMOSIS

IMPORTANCE OF DIAGNOSTIC METHODS, WITH REPORT OF AN EARLY CASE

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and
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A 23-year-old woman had been working in the laboratory at the State Tuberculosis Hospital for about one year. She had been a resident of Kentucky for four or five years, having previously resided in Maryland. Her general condition had always been very good, and she had an uneventful confinement in July, 1959. After about 12 weeks she returned to work and noticed a protracted cold with cough followed by a pleuritic type of pain on the right side. Physical examination did not show any unusual findings. There was no previous record of skin tests as far as the patient could recall.

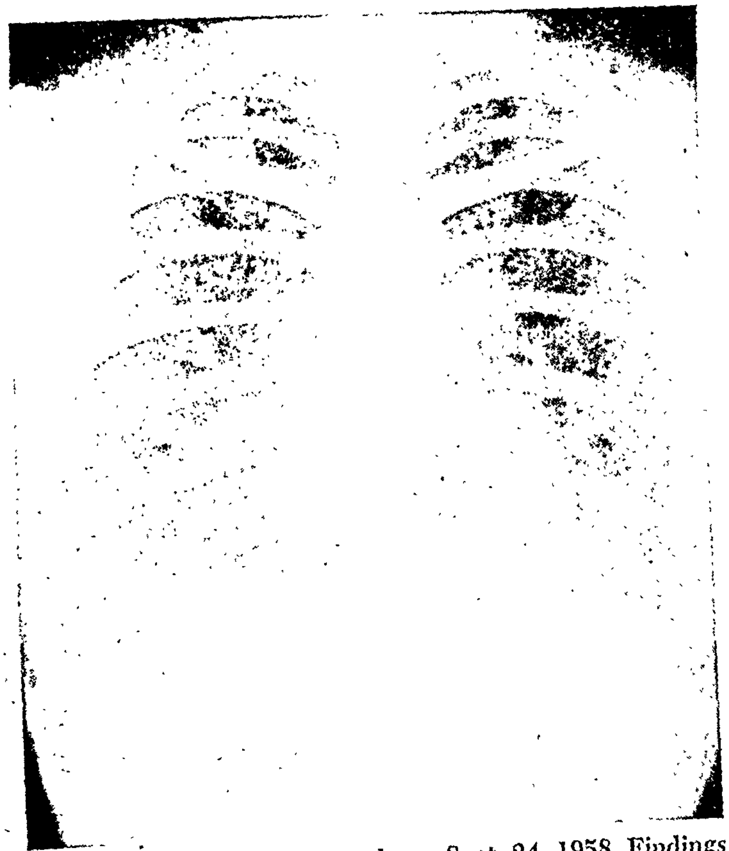

Fig. 1.—Roentgenogram made on Sept. 24, 1958. Findings were reported as "essentially normal," but hilus on right side may be prominent.

A preemployment roentgenogram in September, 1958, showed essentially normal findings (fig. 1). Six months later, on March 5, 1959, a repeat x-ray was obtained which showed a smooth round density just next to the right hilus (fig. 2). The patient was entirely symptom free. She was observed for a further six months after which another roentgenogram was obtained, on Sept. 23, 1959. It showed that the lesion was slightly larger than in the previous film. At the same time there was an onset of symptoms (fig. 3).

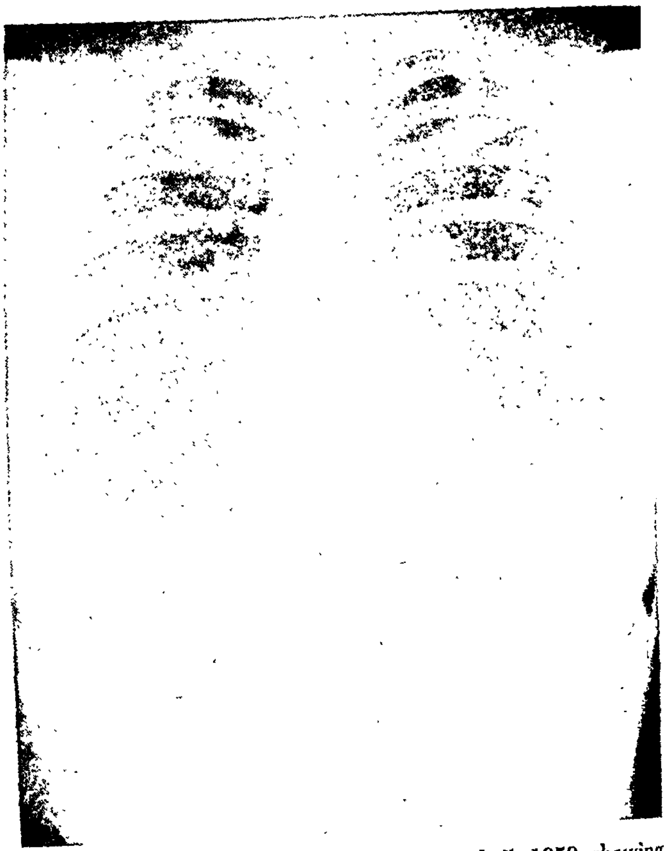

Fig. 2.—Roentgenogram made on March 5, 1959, showing definite smooth mass at hilus on right side. Patient had no symptoms.

Skin tests for purified protein derivative (PPD) intermediate strength and histoplasmin both showed positive results. Tomograms in anteroposterior and right lateral projections were obtained, and these showed clearly a smooth round lesion, about 3.5 cm. in diameter with evidence of central excavation (fig. 4 and 5). In the anteroposterior tomograms it was best seen in the 6, 7, 8, and 9 cm. levels adjoining the right middle-lobe bronchus and also extending posterior to the right main bronchus. A thickening of the lesser fissure was also present, and on the lateral tomograms an area of pneumonitis in the right middle lobe was seen.

The differential diagnosis at this point included pulmonary tuberculosis, pulmonary histoplasmosis, or bronchogenic tumor, either benign or malignant. The pleuritic pain suggested hematogenous dissemination and an infection rather than tumor. The patient had a consultation with a surgeon outside

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From the State Tuberculosis Hospital.

the hospital, and surgery was scheduled to take place in a private hospital.

Meanwhile, blood was submitted for complement fixation reaction for fungi, and the test showed positive results for histoplasmosis, 1/16 in the first antigen and 1/128 in the second antigen. This practically gave the diagnosis away. At thoracotomy about 150 cc. of fluid was found in the pleural space. Fine nodulation over the pericardium and the diaphragm was also seen. A mass of glands was removed from the posterior mediastinum as well as from the depths of the pulmonary fissure. Both of these nodular lesions were found to contain caseous centers. No parenchymal disease could be palpated. A histological diagnosis of tuberculosis was made. However, it is important to note that no acid-fast organisms were found on smear or culture.

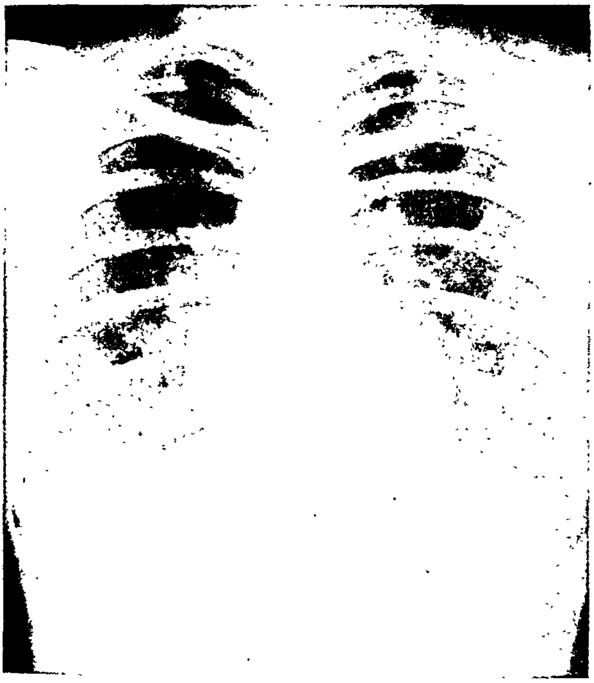

Fig. 3.—Roentgenogram made on Sept. 23, 1959, showing increase in size of mass at hilus on right side. Patient had begun to have symptoms.

Sections of the specimen were submitted to another laboratory (X) center for special staining techniques for fungi, and the diagnosis of Histoplasma capsulatum was confirmed.

It is impossible to discover where this patient might have acquired this infection because pure cultures of H. capsulatum have so far never been obtained in our laboratory.

Comment

We have records of a few patients who were histologically reported to have tuberculosis with no evidence of any tubercle bacilli having ever been isolated from secretions. Sections from these patients were also submitted for special fungus studies, and they were found to be infected by H. capsulatum (see table). In an occasional patient we had several preoperative sputum cultures showing positive results for H. capsulatum, and the pathological diagnosis submitted was still that of tuberculosis. In the patient reported here, waiting for sputum tests to show positive results would have meant a possible risk. There were two divergent opinions: the surgeon and hospital pathologist, on the one hand, still firmly believed that the patient had tuberculosis; the physicians, on the other hand, accepted because of their experience the report of histoplasmosis from the other laboratory. Obviously both views could be right, since occasionally

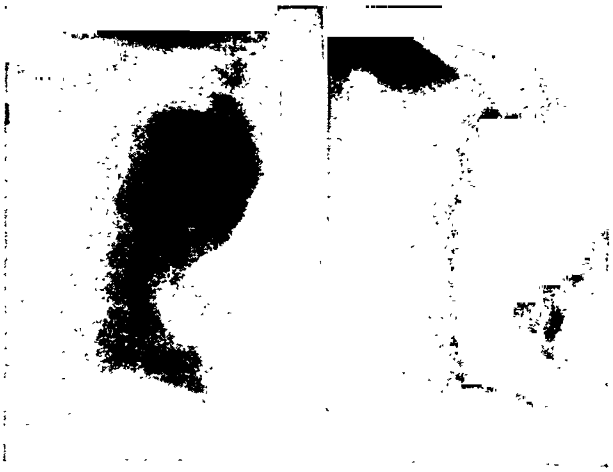

Fig. 4.—Anteroposterior tomogram clearly defining shape and size of lesion with central excavation.

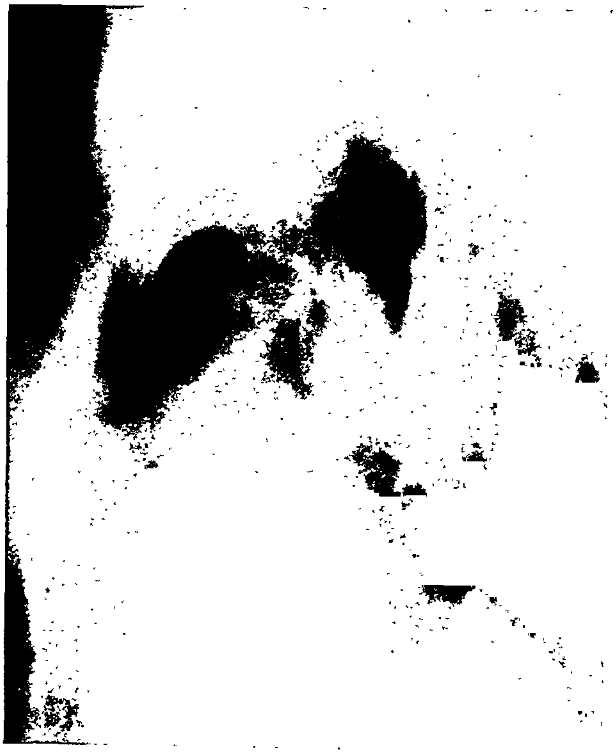

Fig. 5.—Lateral tomogram of right side showing lesion.

tuberculosis and histoplasmosis are found in the same person. In our patient acid-fast bacilli were not found by smear and culture from the surgical specimen, whereas H. capsulatum was recognized, making the diagnosis quite plausible.

Divergence of opinion is again borne out by the cases outlined in the table. Here again the pathological diagnosis of tuberculosis was made by at least three laboratories, but in each case laboratory X submitted a diagnosis of histoplasmosis after they had found the organisms. Thus the getting together of heads of pathology departments would appear beneficial. A uniform policy could perhaps be developed with a view to a better dissemination of present day knowledge regarding the diagnosis of pulmonary fungus diseases. From our limited experience there is no doubt that these conditions are prevalent, but much help from the laboratory is needed for a positive diagnosis.

*Data in Patients with Histoplasmosis which was Diagnosed as Tuberculosis**

Sex	Age, Yr.	Lesion Known, Mo.	Treated as Tuberculosis	Sputum, Examination, Results†	Course	Pathology Report	Organisms *Isolated at* Laboratory X
M	37	64	Yes	Positive for histoplasmosis six times	Surgery	Possibly histoplasmosis or tuberculosis	None
M	56	26	No treatment	...	Died after 2 days	Tuberculosis	H. capsulatum
F	23	7	No	...	Surgery	Tuberculosis	H. capsulatum
F	51	22	Yes	Positive for histoplasmosis four times	Surgery	Tuberculosis; possibly histoplasmosis	H. capsulatum
M	51	>10	Yes	Negative	Surgery	Tuberculosis	H. capsulatum
F	40	36	Yes	Negative	Surgery	Tuberculosis	H. capsulatum
M	33	>32	Yes	Negative	Surgery; relapse	Tuberculosis	H. capsulatum
M	45	>6	Yes	Positive for histoplasmosis four times	Surgery	Tuberculosis	H. capsulatum

* Secretions did not show positive results for tuberculosis in any of these patients.

† The 1st, 4th, 7th, and 8th patients were treated intravenously with amphotericin B 3 times a week.

It has been recorded that the diagnosis of pulmonary fungus disease, especially histoplasmosis and blastomycosis, is being made more frequently now. Other fungus diseases perhaps as yet unrecognized may become more apparent in the future. Thus it would appear important to develop highly effective techniques of isolating and demonstrating the organisms, particularly in areas where such diseases are prevalent. From the clinical standpoint it is also most important not to place the label of tuberculosis on any person who does not have the disease and thus to avoid giving prolonged unnecessary therapy for tuberculosis. Unfortunately not enough emphasis is being placed on the need for bacteriological proof before making the patient undergo prolonged hospitalization and therapy for a presumed case of pulmonary tuberculosis.

Conclusions

The purpose of this report is to make clear the immense importance of bacteriology in making positive diagnosis. Thus therapy for tuberculosis with negative sputum findings in the presence of active disease is unjustified and only evades the issue. This case illustrates only too clearly that even in the absence of positive sputum findings a histological diagnosis can be misleading. The reason for this is the indistinguishable nature of pulmonary tuberculosis and histoplasmosis. The recognition of H. capsulatum requires special staining techniques, and, like all other things, it also requires a certain amount of experience. It is encouraging to see a trend whereby patients suffering from undiagnosed pulmonary diseases are given a greater variety of tests, including those for fungi.

LINACRE.—Dr. Mead began by asking, "What class of men have deserved better of the public than physicians? How much, for instance, does not this country owe to Linacre, the founder of our College? He was perhaps the most learned man of his time, and on his travels was received by Lorenzo de Medici with the most marked distinction. That munificent patron of literature granted him the privilege of attending the same preceptors with his own sons, and Linacre improved the opportunities he enjoyed with great diligence and success. At Florence, under Demetrius Chalcondylas, who had fled from Constantinople when it was taken by the Turks, he acquired a perfect knowledge of the Greek Language.

"He studied eloquence at Bologna under Politian, one of the most elegant Latinists in Europe; and while he was at Rome he devoted himself to medicine and the study of natural philosophy, under Hermolaus Barbarus. Linacre was the first Englishman who read Aristotle and Galen in the original Greek. On his return to England, having taken the degree of M.D. at Oxford, he gave lectures in physic, and taught the Greek language in that university. His reputation soon became so high, that King Henry VII called him to court, and intrusted him with the care of the health and education of his son Prince Arthur."—The Gold-Headed Cane, London, J. Murray, 1828.

COUNCIL ON FOODS AND NUTRITION

Report to the Council

The Council has authorized publication of the following report. This article is part of a nutrition education program which is assisted by the Nutrition Foundation, Inc.

Philip L. White, Sc.D., *Secretary.*

NUTRITION IN CHRONIC RENAL FAILURE

Arthur J. Merrill, M.D., Atlanta, Ga.

Proper management of the patient with chronic renal failure entails a knowledge of how the normal kidney does its work, common kidney function tests and their differential value, chemical abnormalities in chronic renal failure, and chemical derangements in various types of renal disease.

Functions of Normal Kidney

The functional unit of the kidney is the nephron, of which there are roughly two million. Each has a glomerulus with an efferent arteriole, which breaks up into a group of collateral capillaries that rejoin to form the efferent arteriole. Bowman's capsule is a membrane, the visceral layer of which is closely applied to each of the capillaries and the parietal layer of which reflects backward in a cup-like fashion. The base of the cup is continuous with the kidney tubule which undergoes a series of loops and contortions known as the proximal convoluted tubule. This becomes continuous with a long, thin, U-shaped portion called the loop of Henle after which comes the distal convoluted tubule which finally empties into the collecting tubule which drains into the renal pelvis via the collecting duct. The efferent arterioles of most glomeruli break up into a network of peritubular capillaries so that in man the blood supply of the tubules depends to a large extent on the integrity of the glomerular capillaries and arterioles. Shunts and short circuits have not been demonstrated in man.

The glomeruli filter about 180 liters of cell-free, virtually protein-free filtrate, which passes to the proximal convoluted tubules. Here, under average conditions, about 85% of the sodium, chloride, and bicarbonate ions are reabsorbed in essentially the same concentration as found in the filtrate, carrying about 85% of the filtered water with them.[1] The adrenal cortex is thought to exercise a regulatory effect on reabsorption of sodium chloride by the proximal convoluted tubule, probably in the interest of maintaining a normal extracellular fluid volume. Glucose and potassium are normally reabsorbed as is about 57% of the urea.[1] Phosphate is completely reabsorbed at fasting blood levels, but after meals its threshold is exceeded and the excess is excreted.[1] Parathormone, the release of which is triggered by a reduction in blood calcium,[2] increases phosphorus excretion by reducing tubular reabsorption and probably also by increasing filtration rate.[3] Sulfate has a low threshold and small excesses are rapidly eliminated.[1] Much blood calcium is bound to protein and is not filtered. The handling of ionized calcium and the small amount of unionized calcium that is filtered is not well understood. About 90% of the filtered uric acid is reabsorbed.[1]

In addition to its reabsorptive powers, the proximal convoluted tubule excretes phenolsulfonphthalein (P. S. P.), diodrast, para-aminohippurate, sulfonamides, penicillin, and many other substances.

The distal convoluted tubule is supposed to be concerned primarily with acid-base balance and conservation of sodium. Hydrogen ions are exchanged for sodium ions in the formation of carbonic acid from sodium bicarbonate and monosodiumphosphate from disodiumphosphate. The ammonium ion is formed here principally from glutamine and it too is exchanged for sodium ion.[4]

In the distal convoluted tubule, potassium appears to compete with hydrogen ions, so that in potassium ion deficiency hydrogen ions are excreted in excess leading to an alkalosis in the blood and extracellular fluid. In acidosis, when the distal tubules are intact, excess hydrogen ions must be excreted, and under these circumstances some potassium ion retention may occur.[5]

Recent evidence indicates that almost all sodium and potassium ions and perhaps water are reabsorbed by the proximal convoluted tubule and re-excreted by the distal. This requires confirmation, but the evidence is strong.[6]

Thus far, only 85% of the filtered water has been accounted for. Only 0.5 to 1.0% is excreted. The remaining 14% is reabsorbed by the collecting tubules under the influence of antidiuretic hormone (ADH) of the pituitary.[7]

Measurement of Kidney Functions and Clinical Implications

Many patients with advanced renal failure have marked depression of all modalities of renal function. However discrepancies may be detected at

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From the Joseph Scinocca Renal Laboratory, Piedmont Hospital.

times if all tests are done routinely on each person who presents any renal or urinary abnormality. Even more seriously affected patients may exhibit normal function in one or more parts of the nephron. For instance, death may occur from renal failure while the nonprotein nitrogen level (N. P. N.) is still normal. In some instances, tests may disclose the type of disease from which the patient is suffering and may bring about a change in treatment because of alteration in the prognosis.

Tests of Renal Function

Urea or N. P. N. *retention* crudely represents a reduction in glomerular filtration rate (G. F. R.) to about one-third of the normal rate; whereas, a rise in blood phosphorus level indicates that the G. F. R. is about 17% of normal.[8] Chronic glomerulonephritis, the "collagen group" of diseases, amyloid disease, and diabetic nephropathy are primarily glomerular diseases and may cause elevation of the blood N. P. N. level, while other functions may not be compromised until blood flow is disturbed.[9]

Only 20% of P. S. P. is filtered, since the rest is protein bound.[1] The latter has to be removed from the protein and excreted by the proximal convoluted tubular cells. This function depends partly upon rate of blood flow and partly upon integrity of the tubule. An isolated lesion of the majority of nephrons in this segment with good glomerular and distal tubular function is rare. The only instance in which I have seen a normal N. P. N. level, good concentrating power (good function at each end of the nephron), and little or no P. S. P. output in an hour was in a patient with diabetic nephropathy who had true salt-losing nephritis with a normal carbon dioxide combining power. Also, a normal P. S. P. level and an elevated N. P. N. level would pinpoint a lesion in the glomerular filtering membrane, since it would mean an interference with filtration in the presence of a good renal blood flow.[9]

In tubular diseases, such as pyelonephritis, concentrating power is sometimes lost before elevation of N. P. N. level occurs and while P. S. P. output still is good. Acidosis and cation depletion may develop in such instances and may cause death from renal failure without any rise in the N. P. N. level. The blood N. P. N. level may rise in this situation when sodium depletion from tubular disease leads to a fall in G. F. R. In tubular disease also, calcium depletion may provoke parathyroid hormone secretion. This in turn raises phosphorus excretion thus lowering the blood phosphorus, provided the G. F. R. is good enough to support an increase in phosphorus excretion.[2] Tubular disease without much glomerular disease is a condition far more amenable to therapy than glomerular disease, because treatment chiefly entails replacement of losses instead of presenting problems of elimination of retained products as in management of glomerular disease.[9] In chronic renal failure, water retention or edema not caused by heart failure and not associated with low serum protein levels usually suggests either destruction of a large number of nephrons or a primarily glomerular disease and indicates a poor prognosis.[10]

Chemical Abnormalities

Acid-Base Imbalance.—Acidosis is second only to nitrogen retention in frequency of occurrence in patients with chronic renal failure. This is true partly because the end products of protein catabolism are acid and normally eliminated by the kidney, and partly because tubular disease and to a lesser degree glomerular disease cause acidosis. The tubules fail to make ammonia and to exchange hydrogen and ammonium ions for sodium ions. This leaves an excess of hydrogen ions in the blood. Glomerular disease leads to phosphorus retention, which causes acidosis in a more complex fashion.

Alkalosis is rare in untreated patients for reasons given previously.[11] Small excesses of sodium bicarbonate or sodium lactate readily may produce alkalosis since the renal mechanisms for adjusting acid-base balance are damaged.

Water.—Neither an excess nor a restriction of water is handled well by the damaged kidney. Hayman [12] has demonstrated in animals that partial nephrectomy with a normal residual kidney parenchyma causes excretion of a large amount of dilute urine, possibly as a result of a sort of osmotic diuresis produced by the extra load of solids on the remaining nephrons. Merrill [10] found in the same type of experiment that water loads were more slowly excreted by the experimental animal than by the control animals. This inelasticity or lack of adaptability is present in many other functions of the diseased kidney. Inability to elaborate a concentrated urine, plus vomiting and diarrhea lead to water depletion; whereas, loss of total nephrons or the existence of extensive glomerular disease causes water retention. If concomitant sodium ion loss and water retention develop, hyponatremia and sometimes water intoxication will follow. If both sodium ions and water are lost, dehydration and low blood volume may aggravate renal failure even further by depressing the G. F. R.

Sodium Depletion.—The same osmotic diuresis mentioned above may interfere with sodium reabsorption by the tubules. Pure sodium chloride loss, in which the acid-base balance is unaffected, should be a proximal convoluted tubular dysfunction. This is rare as an isolated lesion. However, cation depletion, supposedly a result of a distal convoluted tubular lesion, is quite common. Sodium, the chief cation of the extracellular fluid and plasma, is usually the principal one affected.

Potassium.—Hyperpotassemia or hyperkalemia is not rare in incidences of chronic renal failure, but it seldom becomes a serious problem except terminally when urine flow falls below 500 cc. per day. Merrill advises that no treatment be given since it is either asymptomatic or terminal.[4] However, two of our patients in the few months prior to this writing developed symptomatic potassium intoxication with blood levels of over 8 mEq. per liter and electrocardiogram (EKG) abnormalities in spite of good urine outputs. It appeared that both would have died if potassium-absorbing resin had not been given. Both patients had carried moderately elevated blood potassium values for some time.

Depletion of body potassium and hypokalemia are not infrequent in renal failure stemming from chronic pyelonephritis. Tubular damage with a breakdown of base-conserving mechanisms may cause loss of sodium, potassium, calcium, and magnesium cations in pyelonephritis. Potassium-losing nephritis per se is a rare condition.[13] Conn [14] believes that most, if not all, of such cases are really examples of hyperaldosteronism. The consequent hypokalemia may produce vacuolar degeneration of the tubules with loss of tubular concentrating power, as well as a fall in the G. F. R. and reduced ability of the tubules to excrete diodrast, para-aminohippuric acid (PAH), etc.[15] This is said to be a completely reversible lesion if the potassium ion is repleted.

Phosphate and Calcium.—The inorganic phosphate level of the blood rises in renal failure if the G. F. R. falls below 17% of normal.[8] However, if tubular insufficiency without glomerular insufficiency is present and calcium depletion follows, the parathyroid glands are stimulated by the low blood calcium level. This in turn causes a phosphate diuresis and often a low blood phosphorus level, provided the G. F. R. is high enough to permit it. If, however, the glomerulus is sufficiently injured, the phosphate diuresis cannot occur and the blood phosphorus level remains high.[2]

The behavior of calcium ion in renal failure is mysterious. Why phosphorus "gets the upper hand" and calcium becomes depleted is not thoroughly understood. In cation-losing nephropathy, calcium would be lost. Another factor perhaps, is that calcium is not absorbed well from the digestive tract in renal failure.[2] Retention of phosphorus is a third reason, but is not necessary for development of hypocalcemia.

Magnesium.—The importance of magnesium in the symptomatology of chronic renal failure has not been sufficiently clarified at the present time. There is little doubt that it plays an important role, which will become apparent as magnesium determinations become available in the average hospital laboratory.

Nutritional Factors in Production

Vitamin D intoxication [16] and the milk-alkali syndrome [17] are associated with a renal lesion that eventually leads to death if aggravating factors are not withdrawn. Large doses of vitamin D, as are used by some physicians in treating arthritis, may, over a period of time, terminate in metastatic calcification and renal failure. Prolonged ingestion of three to four quarts of milk per day, along with some form of alkali such as Sippy's powders, may lead to a similar condition. It is not certain whether large amounts of milk alone can produce the same difficulty. The history, plus the physical finding of a band of keratitis around the limbus, along with an elevated blood calcium level and a high or normal blood phosphorus level, suggests the diagnosis. When the blood phosphatase level is normal and urinary excretion of calcium is not increased, these features aid in distinguishing this syndrome from hyperparathyroidism.[17] Withdrawal of the offending substance or substances may cause disappearance of the renal failure, but more often it is so well advanced that it can only be arrested. Several of Burnett's patients eventually died despite the withdrawal of milk and alkali. One of Wood's patients with hyperparathyroidism had an N. P. N. level of 90 mg. per 100 cc. at the time that the tumor of the parathyroid was removed. Seventeen years later the patient's N. P. N. level was still 90 mg. per 100 cc.[18]

Digestive Organs in Renal Failure

Fibrinoid degeneration of the blood vessels in the digestive tract produces ischemic and hemorrhagic lesions that form a fertile culture medium for bacteria, especially in the colon. Stomatitis and esophagitis are often found, and may interfere with the oral intake of food. Nausea, vomiting, and diarrhea lead to loss of electrolytes that must be replenished. Vomiting is frequent and often can be controlled. Diarrhea is less common and is more difficult to regulate.

Treatment

The vigor with which treatment should be pursued is determined by the responsiveness of the underlying lesion to therapy and the success with which chemical abnormalities can be combated. In general, responsiveness to therapy of glomerular disease with hypertension and edema combined is less than that of tubular lesions. Pyelonephritis may occasionally respond to antibiotics, particularly if evidence of active infection is still present and if the radiological silhouette of the kidney is not contracted seriously. Chemical changes associated with glomerular disease are less susceptible to treatment because they involve retention of substances that have to be eliminated, while tubular lesions involve losses of electrolytes that can be added to the daily intake with relative ease.

Aims of Treatment

Protein catabolism should be reduced by supplying ample calories from other sources. Use of anabolic hormones, such as testosterone is impractical in chronic renal failure because of the side-effects; however, norethandrolone (Nilevar), a new anabolic preparation, is said to be of value and has no unpleasant side-effects.[19] Since poor concentrating capacity of the tubules increases the quantity of water needed to excrete the body's daily quota of 40 Gm. of solids, dehydration should be avoided. Dehydration may also shrink the blood volume and cause a reduction in the G. F. R. However, overhydration will aggravate or precipitate nausea, vomiting, and diarrhea, and may cause convulsions or congestive heart failure. Dilution of the blood sodium may bring about a fall in G. F. R. Avoid diamox, methionine, and acid salts since acidosis is already present. The damaged kidney has no defense against these substances because the tubules have lost their capacity to increase ammonia production. Correct acidosis and osmolarity to the degree most consistent with the patient's comfort and well-being. This must not be done rapidly since time must be allowed for internal adjustments in electrolytes to take place. Correct electrolyte depletions to the levels conducive to the optimal function of the kidney and of body economy. Maintain nutrition and weight at as nearly a normal level as is possible. Control undesirable losses of electrolytes and water from vomiting and diarrhea. Maintain appetite and morale.

Procedure

Water.—Water balance can scarcely be considered adequately except in relation to sodium. An intake designed to produce a urine output of from 2,500 to 3,000 cc. daily is desirable, provided no excess water or edema accumulates. Fluid retention is apt to occur in hypertensive patients or in those with glomerular disease or advanced renal failure from extensive loss of entire nephrons.[10] Careful observation of fluid intake and output and daily determination of weight will provide early warnings of overloading. If the sodium intake is known to be enough for the particular subject under study and the blood sodium concentration begins to decrease, then the patient is getting more water than his kidneys can handle successfully. If the patient has pitting edema over the back and the blood sodium level is low, he is obviously retaining an excess of water over sodium, since sodium excess per se could not be causing edema in such a situation. There is a great amount of emotional resistance among many physicians to restricting water in the presence of renal failure, but I have done it in quite a few patients and the ability of the kidneys to excrete solids has actually improved. An improved sensorium and sense of well-being were achieved also. Some patients may need to be restricted to as little as 800 to 1,000 cc. daily. While increased intake may increase the output of water, not all ingested excess is excreted and some retention occurs. Under such circumstances, the output of solids actually may decrease.

On the other hand, if the patient becomes edematous and the blood sodium concentration is normal or near normal, excess water must not be eliminated by restriction of fluids any faster than sodium is excreted, or a serious rise in blood sodium concentration may ensue.

Sodium.—The normal daily sodium chloride intake is about 9 Gm. or roughly 150 mEq. Sodium regulation is important since sodium is the chief cation of the extracellular fluid and blood, and is the principal determinant of extracellular fluid osmolarity. After two or three days on a low sodium intake, a normal subject will excrete a urine that is virtually free of sodium. If a 24-hour urine specimen collected from such a person contains 25 mEq. or more of sodium, then the patient is not able to conserve sodium properly. He may lose even more sodium in his urine if his sodium stores are raised to normal and the 24-hour excretion now will give some indication of what the patient's intake should be.

Both sodium restriction and sodium excess are poorly tolerated by the patient with renal failure. The average requirement will be from 4 to 5 Gm. of sodium chloride per day. If acidosis is present, salt can be restricted and sodium bicarbonate may be given instead. When larger amounts appear to be necessary, a 24-hour urine sodium excretion should be determined and proper intake calculated from that. A high blood chloride level in the presence of a normal blood sodium level usually means water dehydration plus sodium depletion, and an intake of both water and sodium bicarbonate would be indicated. Occasionally, as in salt-losing nephritis, quantities of sodium chloride up to 35 Gm. per day are necessary to prevent salt depletion and shock.[20] This, however, is a rare disease; whereas cation-losing disease including sodium is fairly common. The quantity lost in the latter is usually less, often from 4 to 6 Gm. per day in excess of normal sodium intake.

In the hopelessly advanced renal failure victim, proper management of sodium and water can mean a quiet somnolent death as opposed to a horrible one associated with dyspnea, mania, and convulsions. Reduction of water and sodium stores below normal produces somnolence, while an excess may cause dyspnea and overactivity. An excess of water may precipitate nausea and convulsions.

Acidosis in many patients may be completely corrected with sodium bicarbonate but in some, particularly those with edema, the patient fares better with only partial restoration of the blood HCO_3 to normal—about 15 to 20 mEq. per liter (33 to 44 vol. per 100 cc.). When cation loss is the chief problem, especially with calcium deficiency and fractures or pseudofractures, acidosis must be fully corrected. About 3 to 6 Gm. of sodium bicarbonate will usually suffice. Sometimes a change of 1 Gm. per day over a period of time will make the difference between acidosis and alkalosis. Therefore, careful rechecking must be done until the carbon dioxide-combining power is properly adjusted. Reduction in neutral salt or sodium chloride may be necessary to avoid giving too much sodium ion while adjusting acid-base balance.[9]

Potassium.—The normal daily intake of potassium is from 50 to 90 mEq. As stated, the blood potassium level and body content of potassium may be either depressed or elevated in renal failure. A blood potassium determination is necessary in deciding upon proper management. When urine output drops below 500 cc. per day terminally, potassium intoxication is not unusual. Even at other times elevation of the blood potassium to 6 to 6.5 mEq. per liter may persist for many months without EKG changes or production of symptoms. Some authorities[4] feel that no treatment is necessary and this certainly is correct in most instances. However, in three patients, I have observed a fairly rapid increase to toxic levels associated with advanced EKG changes despite an ample urinary output. It is a simple matter to keep the blood potassium level at a normal concentration with one to four teaspoonfuls of potassium-absorbing resin and this may be the safest procedure. An occasional check is needed to be sure that the blood potassium level is not reduced too much.

Hypokalemia is of great importance because it can lead to further deterioration of renal function from kaliopenic (hypopotassemic) nephropathy and can result in myocardial damage that at times may be permanent. Hypokalemia is most often seen in patients with pyelonephritis and may threaten life without elevating the blood N. P. N. level.[21]

Even when potassium deficiency is present, the physician must bear in mind that the damaged kidney may not be able to excrete a large amount of potassium so that deficits must be made up cautiously. Unless the patient is unconscious or has uncontrollable vomiting, oral administration is the safest. If potassium is given intravenously, a maximum concentration of 40 mEq. per liter (3 Gm. of potassium chloride) of a fluid containing glucose should be given over a two hour period. Greater concentrations require constant observation to be sure that the rate of administration is not increased inadvertently. If the deficit has occurred over a long period, there is no emergency since either the renal damage or the prolonged deficiency operates in some fashion to prevent further severe loss of potassium until the deficit is replenished.[15] In chronic cases, from 3 to 6 Gm. of added potassium salts by mouth daily will suffice. In rare instances, larger amounts will be required.

Calcium and Phosphorus.—Blood calcium, as a rule, becomes depressed in chronic renal failure. Symptoms, however, are rare because acidosis promotes ionization of calcium. Only when acidosis is corrected too rapidly does tetany become apparent. Hypokalemia, by reducing neuromuscular irritability, may prevent tetany and the latter may appear as the potassium deficit is remedied. Oral calcium per se has no effect in chronic renal failure unless associated with correction of other abnormalities. Retention of phosphorus may be treated by reduction of phosphorus intake and/or administration of 120 cc. of aluminum hydroxide gel. If blood phosphorus level is low or normal and hypocalcemia seems to be related to acidosis, then correction of acidosis is the only means whereby the calcium deficiency can be eliminated. After acidosis is controlled, recalcification of the bones can and should be hastened by administration of oral calcium and vitamin D.[2] This applies in Milkman's Syndrome and the de Toni-Fanconi Syndrome.

Other Electrolytes.—Chloride seems to be juggled back and forth in acid-base balance and is of no importance in itself. A high blood chloride level and normal blood sodium level without unusual ingestion of chloride ions generally means sodium plus water depletion. This can be corrected by giving sodium bicarbonate, sodium lactate, or sodium citrate with water. An example of this condition is the hyperchloremic acidosis found in patients with ureterosigmoidostomy and pyelonephritis.

Sulfate is probably of considerable importance in the symptomatology of renal failure because of its role in the production of acidosis and because a high blood sulfate level may provoke tetany in the presence of normal blood calcium and phosphorus levels. Theoretically, barium should be the only substance which removes sulfate since it is the only insoluble sulfate salt, but, unfortunately, all other barium salts are toxic so that none can be used to help eliminate sulfate through the stool.

Protein.—The problem of protein intake in chronic renal failure is a knotty one particularly with respect to amount. Estimates by authorities vary from almost no protein content in the butter-sugar-cornstarch diet of Borst,[22] to 20 Gm. of protein per day in the rice diet suggested by Kempner,[23] and 1 Gm. of protein per kilogram per day in the diet as suggested by Burnett. Pros and cons of these diets have been discussed elsewhere[24] and will not be considered here. The minimum for wear and tear replacement is 0.5 Gm. of protein per kg. of body weight,[4] with additional allowance for losses due to proteinuria, or stress. For patients with an N. P. N. level of 150 mg. per 100 cc. or more, I usually allow an intake of 35 Gm. daily. If the N. P. N. level is stabilized and below 100 mg. per 100 cc. the patient is started on 50 Gm. of protein daily.

Type of protein is almost as important as amount (see table). Proteins used should contain all essential amino acids for formation of tissue. The body does not store aminoacids, and all that are not used are excreted immediately in the urine, thus adding to the load upon the kidney.[25] Vegetable proteins have biological values of only 60 to 70 as opposed to a value of 90 for animal protein, but the great variety of vegetables normally eaten enables a sufficient number of essential amino acids to get together at once to form tissue. Those that are not utilized are thrown off by the kidney before the next meal. A variety of food is less likely to be ingested by the patient with renal failure so that he needs meat, eggs, milk, cheese, or soybeans, all of which have biological values of around 90.[26] This leaves little waste to be excreted by the kidney. A diet too low in protein tends to loss of appetite.

About 0.5 Gm. per kilogram of body weight per day seems to be the proper intake for the patient with severe renal failure. Larger amounts are given to those with better function. In experimental animals this intake reduced the excretion of protein catabolites, but has not been adequately tested in patients with renal failure.

Carbohydrate.—Aside from taste, carbohydrate has another important function in the diet of the person with renal failure, which is its protein-sparing action. Raising carbohydrate intake above 100 Gm. in normal subjects failed to produce much more protein-sparing action in six to eight days than the 100 Gm. carbohydrate diet.[27] However, there is reason to believe that over a period of 20 days or more, adaptive processes take place which enable the body to utilize much more carbohydrate, particularly if the subjects are on an extremely low protein diet.[22a] Therefore, 300 to 400 Gm. of carbohydrate are given daily if the patient can take it. Carbohydrate and protein should be taken at the same time, as this increases utilization of amino acids.[28]

Menu for Diet Containing Approximately 2,200 Calories, 50 Gm. Protein, and 4 Gm. Salt†*

Breakfast
- 1 large glass fruit juice or large serving fruit
- 1 slice toast with 1 teaspoon butter and 1 tablespoon jelly
- 1 serving cereal (hot or cold) with 3 oz. heavy cream and sugar
- 1 egg with 1 teaspoon butter
- Tea or coffee with cream and/or sugar

Before lunch: 4 ounces sherry

Lunch
- Sandwich
  - 2 slices bread
  - 1 ounce meat
  - 1 teaspoon butter
  - 1 teaspoon mayonnaise
- Tossed salad with 2 tablespoons French dressing
- Large serving fresh or canned fruit
- Tea, coffee, or carbonated beverage

Before dinner: 4 ounces sherry

Dinner
- 3 ounces meat with gravy
- 1 average serving potato with 1 teaspoon butter
- 1 serving vegetables with 1 teaspoon butter
- Vegetable salad with 2 teaspoons mayonnaise
- Large serving fresh or canned fruit
- Tea, coffee, or carbonated beverage

Bedtime
- Large glass fruit juice or carbonated beverage
- 2 graham crackers with 1 tablespoon jelly

Food Content

Food‡	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Sodium Mg.
1 large fruit	10	..	..	2
1 slice toast, regular	15	..	..	170
1 t. butter	..	..	5	50
1 T. jelly	6	..	..	...
1 serving cereal	15	2	..	10
3 oz. heavy cream	..	..	30	36
1 t. sugar	5	..	..	...
1 egg	..	7	5	40
1 t. butter, regular	..	..	5	50
1 oz. light cream	..	..	5	9
1 t. sugar	5	..	..	...
4 oz. sherry	17	..	..	...
2 slices bread, regular	30	4	..	340
1 oz. meat	..	7	5	20
1 t. butter, regular	..	..	5	50
1 t. mayonnaise	..	..	5	90
Tossed salad	..	..	..	9
2 T. French dressing	..	..	10	...
Large fruit	20	..	..	2
Carbonated beverage	10	..	..	...
4 oz. sherry	17	..	..	...
3 oz. meat	..	21	15	60
2 T. gravy	..	..	10	...
1 serving potato	15	2	..	1
1 t. butter	..	..	5	50
1 serving vegetable	7	2	..	9
1 t. butter, regular	..	..	5	50
Vegetable salad	..	..	..	9
2 t. mayonnaise	..	..	10	180
Large fruit	20	..	..	2
Sugar (tea)	5	..	..	...
Large fruit	20	..	..	...
2 crackers	15	2	..	...
1 T. jelly	6	..	..	...
Totals	238	49	120	1,239

Total Calories 2,293

* From Merrill, J. P.: Treatment of Renal Failure, New York, Grune & Stratton, Inc., 1955.

† Salt may be used sparingly in cooking and none to be added at table. A salt content of 4 Gm. is given only as an example, since, as noted in the text, patients with renal failure may require a high salt intake. This must be individualized and may be increased by table salt and other sodium supplements without increasing protein content.

‡ T.—tablespoon; t.—teaspoon.

Further protein anabolism is encouraged by the use of testosterone. Norethandralone has a similar action without the masculinizing action of testosterone.[29] New work on the mechanism of the protein-sparing action of carbohydrates suggests some exciting possibilities. Generation of certain co-factors during glycolysis greatly accelerates protein synthesis.[30] It is possible that these co-factors may be used eventually to promote protein building.

Fat.—Fat supplies 9.0 calories per gram, or more than twice as many as do carbohydrate and protein. Thirty-five to 40 Gm. of protein and from 300 to 400 Gm. of carbohydrate will yield 1,340 to 1,800 calories. If the average diet is 2,000 to 2,500 calories, the fat content will need to be about 75 to 90 Gm. per day.

There is no evidence that fat is essential to man, although it is known to be essential to animals. Nevertheless, it reduces the specific dynamic action of protein probably by slowing absorption and permitting the proper amino acids to "find" one another.[4] In rats, it diminishes the use of protein. In preliminary studies, Meng has shown a 30% increase in protein-sparing from intravenous fat. If later work confirms his findings, the present concept that fat has no protein-sparing action aside from slowing its absorption will have to be modified.

High fat diets such as the Borst diet are nauseating to the average patient and may provoke a diarrhea. Merrill[4] believes that the patient burns so much of his own fat that the high fat intake is unnecessary. Certainly it is undesirable for prolonged usage in the chronic renal failure subject, especially since many individuals are prone to the development of arteriosclerosis.

Summary

Management of chronic renal failure involves a knowledge of the various chemical abnormalities that are likely to occur with different types of renal disease. In general, glomerular diseases such as glomerulonephritis, the "collagen" group, diabetic nephropathy, and amyloid disease tend to cause retention of sodium chloride, water, nonprotein nitrogen, phosphate, and sulfate. Chronic tubular diseases with acidosis, such as pyelonephritis, lead to loss of cations such as sodium, phosphorus, calcium, and magnesium. In glomerular disease alone, a diet low in protein (from 35 to 50 Gm.) or low in nitrogen, potassium, sodium, phosphate, and sulfate is required. Water must be restricted so as to prevent dilution of sodium ion with resulting further fall in filtration rate and further diminution in excretion of solids. In tubular disease, lost cations such as sodium, magnesium, and calcium ions

must be replaced. These patients usually cannot tolerate restriction of sodium below 4 Gm. of sodium chloride or sodium bicarbonate unless water output drops below 1,500 cc. daily as in combined glomerular and tubular disease. Acidosis usually should be corrected fully in patients with pure tubular insufficiency. In combined glomerular and tubular disease, the 24-hour excretion of water, sodium, and other electrolytes may have to be measured at partly or fully corrected blood levels to determine the proper daily intake. Full correction of acidosis is seldom advisable. Daily records of weight are useful in calculating the ideal water intake. A urine output of 3,000 cc. daily is ideal, provided water retention is absent. Toxic substances usually excreted by the kidney such as streptomycin and other antibiotics, and certain sedatives should be avoided or given with caution. Acid salts, such as ammonium chloride and sodium biphosphate must be avoided since most patients are already acidotic. Drugs producing sodium loss, such as diamox and potent diuretics, must be used only with extremely careful chemical control and then only in milder cases of renal failure. With retention of phosphorus, restriction of phosphate (milk and eggs) must be practiced, unless it can be controlled by aluminum hydroxide administration (120 cc. daily). In occasional chronic cases, retention of potassium may require administration of a sodium carboxylic resin. Terminal patients, who have a low urine output, often need the resin. The best diet for the average patient with advanced renal failure consists of 35 to 50 Gm. of chiefly animal protein, 4 Gm. of salt (or 2 Gm. of sodium chloride and 2 Gm. of added sodium bicarbonate), 70 Gm. of fat, and from 150 to 400 Gm. of carbohydrate.

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THE JOURNAL
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MEASLES VACCINATION

UNTIL Enders isolated the measles virus in tissue culture a few years ago, little was accomplished toward prevention of this disease, despite its high incidence throughout the world. The epidemic described by Hoekenga and others in this issue of THE JOURNAL, (page 868), providing evidence that measles can be a severe and sometimes fatal disease, serves to emphasize its medical importance.

In developing a new immunizing agent for a disease such as measles, the long-range aspects as well as the immediate results must be considered. If a vaccine produces immunity for a relatively short time, then revaccination at intervals is necessary to maintain an immune population. In time, if reimmunization should be discontinued, a susceptible adult population would develop in which the disease might often be more severe than that experienced during childhood. A situation of this type might occur after use of an inactivated, or killed, virus vaccine, even though some vaccinated individuals might maintain immunity from natural "boosters" through exposure to virulent virus. There is much evidence to indicate that immunity of longer duration can be obtained with an attenuated, or modified, live virus vaccine. Even if lifelong immunity is not produced, it seems certain that the antibody response would be of sufficient magnitude so that fewer revaccinations would be required to maintain an immune population.

Two basic approaches may be followed in developing live virus vaccines. One involves selecting a virus from one host which will create immunity to a specific disease in another species, such as the use of cowpox virus to protect humans against smallpox. The other procedure is to utilize laboratory techniques to alter the virulence of the disease-producing virus so that it is still capable of immunizing the host but is markedly reduced in ability to produce disease. The 17D strain of yellow fever, used as an attenuated live virus vaccine for the successful protection of many thousand people, best illustrates the latter approach. Further support for the use of modified live virus vaccines is provided in veterinary medicine, where a number of such products have been effective in preventing serious infections in animals.

The two reports in THE JOURNAL, (page 861, 868), describe investigations in which both types of modified live virus vaccines were used for the prevention of measles. One approach utilized the principle mentioned previously for smallpox, in which the serological relationship between canine distemper virus and measles was exploited. Although preliminary work indicated this had some merit, tests in monkeys and humans showed that, with this strain of distemper virus, there was not enough immunological relationship to make a vaccine of practical value. This does not mean, however, that subsequent studies with other strains of distemper virus might not be more fruitful. The other study deals with efforts to reduce the virulence of measles virus sufficiently to eliminate disease, yet provoke a good antibody response, similar in some respects to investigations reported by Enders and Katz. It is important to note that a vaccine incorporating this modified virus was found to be of significant value in preventing measles in vaccinated volunteers when tested in a large field trial during a measles epidemic. Although reactions to the vaccine were far less severe than illness associated with natural disease, additional modification of the virus is desirable. However, since this modified virus does not spread from inoculated to uninoculated individuals, the vaccine could be considered of value in its present state of development for epidemics or high-risk situations.

It is also noteworthy that this modified live virus vaccine produced antibody levels comparable to those obtained in humans after recovery from measles. Presumably, then, immunity after vaccination with this agent would have the same lasting properties as that induced by natural infection.

If future investigation demonstrates the feasibility of further reduction in virulence without loss of immunological response, the medical profession can optimistically await the availability of an innocuous and effective prophylactic vaccine.

THE MUNIMENTS OF THE M. G. H.

The history of a hospital is essentially a document of individual achievements, clinical, scientific, and sociological. The story of the Massachusetts General Hospital, a peer among the great private teaching hospitals in America, has been told in five volumes published in chronological order during the past 100 years.[1] The last volume has been prepared by Dr. Nathaniel W. Faxon, Director Emeritus, and embraces the period 1935-1955.[2] According to Francis C. Gray, Chairman of the Board of Trustees, this period "saw the trinity of the care of the sick, teaching and research unite, for the good of mankind as never before in history of any hospital." The M. G. H. was founded in 1811; it will be 150 years old in 1961. "It was organized to afford hospital care for the sick, to provide the

Harvard Medical School with a place to teach medical students at the bedside, and through this joint endeavor, to advance medical knowledge. The undertaking with the Harvard Medical School, operating more actively today than perhaps at any time in its long history, has been of outstanding significance in the growth and development of the hospital."

When the plans for the M. G. H. were under study, there were few hospitals in America that provided a precedent for guidance. The Pennsylvania Hospital in Philadelphia, the New York Hospital in New York City, and a few government hospitals made up the entire list on this side of the Atlantic. The Presbyterian Hospital in New York City was not established until 1872[3]; the Johns Hopkins Hospital in Baltimore was founded in 1891. The M. G. H. was a pioneer chronologically and philosophically, irrespective of the decision on Judgment Day about the validity of other claims to the initial exhibition of ether in surgical anesthesia under the Bulfinch Dome.

The destiny of the M. G. H. has been guided by the skillful hands of friendly people since its founding. During the years described by Faxon, the members of the Board of Trustees, the administrative staff, and the professional staff, respectively, have assumed leadership for privately endowed teaching hospitals with outstanding achievements. The Rt. Rev. Henry Knox Sherrill, recently retired Presiding Bishop of the Protestant Episcopal Church in the United States, was a member of the Board of Trustees from 1928 to 1946 and Chairman of the Board for his last 11 years in office. In spite of many canonical responsibilities, Bishop Sherrill gave of his time and effort to the M. G. H. in unlimited quantity. Regular attendance at scheduled Board meetings constituted but a small part of his devotion to the hospital. He lived with the hospital as he lived with his church.

The intimate association with Harvard Medical School and the dual appointment system of school and hospital insured an enviable array of skilled and talented physicians, leaders in American medicine. Bedside teaching has been excellent at the M. G. H. during the past two generations and has shared honors with clinical investigation and the pursuit of basic research. In the last category, it may be noted that Dr. Fritz Lipmann, a recipient of the Nobel award in chemistry for his discovery of coenzyme A, was associated with the surgical research laboratory at the hospital for more than a dozen years. The other Nobel laureate of the M. G. H. family was Dr. George R. Minot, initially a house pupil and later a member of the Board of Consultation.

In war and disaster, as well as in less harrowing experiences, the M. G. H. has been ready at all times to serve. The hospital cared for many casualties in the Cocoanut Grove fire in Boston on November 28, 1941. It is noteworthy that the Trustees of the hospital assumed all costs for the care of the Cocoanut Grove patients during the first fortnight of hospitalization. At the time the M. G. H. Unit of the Sixth General Hospital was in training at Camp Blanding, Fla., and the impact of the disaster, because of the shortage of professional staff, was especially grave.

No more convincing evidence of the side-by-side significance of clinical medicine and clinical research at the M. G. H. can be offered than the mention of two notable firsts in medical education, Ward 4 and the Cabot cases. Ward 4 is the metabolism ward at the M. G. H. It was planned in principle after the Lusk-Dubois unit at Bellevue Hospital but served quite a different function. A great variety of diseases were studied on Ward 4 by full-time investigators as well as practicing physicians. It is customary for most university teaching hospitals in America today to have a metabolism ward, frequently patterned after Ward 4. The other innovation, the reporting of cases, was begun by Richard Cabot in 1895. They were edited and assembled in the early years in a two-volume treatise entitled "Differential Diagnosis." In 1920 the *New England Journal of Medicine* began the publication of the cases on schedule. The publications were expanded by Dr. Tracy B. Mallory in 1933 and identified subsequently as the Case Records of the M. G. H. Dr. Benjamin Castleman is the current editor of these outstanding discussions that encompass a large area in clinical medicine and surgery.

Faxon has not ignored finances, a *sine qua non* of a teaching hospital. In 1935 the total research expenditure was slightly greater than $52,000. Expenditures for research in 1957 exceeded $3,000,000. Over the same period the cost per day of hospital care increased from $6 to more than $24. The size of the M. G. H. capital endowment was wisely omitted from the history. A review of the recent annual report of the hospital, however, reveals a sum handsome in size but surely carefully invested and the income prudently used. As an example, the report of the Trustees of 1950 stated: "Four actions were taken by the Trustees to strengthen the organization and financial base of the hospital. The first of these was a vote approving in principle the use of the hospital's *general funds for education and research* in any instance where such use might be thought advisable."

In cogitating over this editorial, it was expected that this last paragraph would list a few notable names selected from the several departments of the M. G. H. over the 20-year period. When selection became imperative, it was obvious that no paragraph would hold the names of the illustrious

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1. (*a*) Bowditch, N. I.: History of Massachusetts General Hospital, 1811-1851, privately printed, 1851. (*b*) Ellis, G. E.: Second Edition of Bowditch with Continuation to 1872, printed by the Trustees, 1872. (*c*) Myers, G. W.: History of Massachusetts General Hospital, 1872-1900, Griffith-Stillings Press, Boston, 1929. (*d*) Washburn, F. A.: Massachusetts General Hospital—Its Development, 1900-1935, Boston, Houghton Mifflin Company, 1939.

2. Faxon, N. W.: Massachusetts General Hospital, 1935-1955, Cambridge, Mass., Harvard University Press, 1959.

3. Lamb, A. R.: Presbyterian Hospital and Columbia-Presbyterian Medical Center, 1868-1943: History of Great Medical Adventure, New York, Columbia University Press, 1955.

physicians, surgeons, pathologists, neurologists, psychiatrists, *und so weiter*, listed on the 22 pages of the appendix of Faxon's history. The M. G. H. roster is a small "Who Is" in American medicine.

HISTOPLASMOSIS

Histoplasmosis has been regarded by most medical practitioners as somewhat of a curiosity which has received a great deal of publicity in recent years, but which they themselves rarely see. It is becoming increasingly clear that the severe manifestations of the disease are far from infrequent and, indeed, must be considered by practitioners and specialists throughout the entire country. The pediatrician has become increasingly aware of the frequency of severe pulmonary involvement and hilar lymphadenitis with atelectasis associated with infections caused by Histoplasma capsulatum. It also appears that the disease disseminates more frequently in young children, and this dissemination must be recognized and treated early to avoid a fatal outcome.

The internist must consider a possible diagnosis of histoplasmosis in all cases of chronic or unresolving pneumonia, and especially in cases of Addison's disease which is not infrequently caused by histoplasmosis. Nose and throat specialists must be increasingly on the lookout for involvement of the vocal cords and larynx with H. capsulatum. The specialist in tuberculosis and those dealing with chronic chest disease must be increasingly aware of the problem of chronic cavitary histoplasmosis, as it is now estimated that more than 3,000 cases of active cavitary histoplasmosis are resident in our tuberculosis sanatoriums at the present time.

The problems of histoplasmosis relating to the surgeon are becoming increasingly complex. As stated elsewhere in The Journal, (page 875, 878), it has become clear, on the basis of numerous reports, that histoplasmomas are probably the most frequent causes of coin-shaped lesions so frequently confused with pulmonary cancer. This article aptly stresses the lack of symptoms, the frequent absence of calcification, and the dangers of protracted delay before surgical intervention. Another feature stressed in this article is the fact that about 20% of the patients operated on still complained of symptoms two to seven years after operation. In other words, the thoracotomy is not to be lightly undertaken, without proper education of the patient. Lastly, two of the patients described in the article had reactivation and developed chronic progressive histoplasmosis three and four years after operation. Surgeons are also concerned with more chronic and intricate forms as well as histoplasmomas of the lungs. Reports are increasing that chronic constrictive mediastinitis, with or without superior venal caval obstruction, occurs after histoplasmosis and is an extremely difficult and complicated surgical problem to handle. In addition, several recent reports of constrictive and fibrous pericarditis caused by histoplasmosis have further implicated this organism as a cause of chronic fibrous reactions within the chest.

The practitioner should be aware of the usefulness not only of the skin test, as stressed, but also of the serologic tests which are available through the laboratories of the local or state health department. Since serologic tests are positive only during active disease, its value in diagnosis is obvious.

The practicing physician must be continually alert to the fact that, although histoplasmosis is common and usually acute, it can also be severe and chronic. Many problems of the frequency and manifestations of the severer types of the disease remain to be elucidated. Amphotericin B has proved to be a reasonably effective antibiotic in the severe type of the disease, but it is somewhat difficult to use. However, it is clear that some progress is being made in the therapy of the disease.

FACTORS TO BE CONSIDERED IN SURGERY FOR CLOSURE OF VENTRICULAR SEPTAL DEFECTS

The high standards set by the American Heart Association's committee for "Standards of Care for Patients with Congenital Heart Disease"[1] are extremely timely because of the widespread feeling in the United States that a child with an operable malformation should have the condition corrected. There is also the feeling that, because there are many children with such defects, it is urgently necessary to operate promptly.

Although an ever-increasing number of malformations can be corrected by surgery, it does not mean that every child with a correctable malformation should have immediate surgery. Haste makes waste! In this instance, haste means needless loss of life. For many children, an operation is not urgent. It is wrong to say the child must have an operation or he will die. None of us is immortal, but there are many children with malformations of the heart which are entirely compatible with a long and active life; such children are in no need of surgery.

Broadly speaking, the less serious the condition, the lower is the risk of operation. However, this does not mean that operation is indicated or justified because the patient is a "good risk." "Risk" means there is danger. The danger involved in the operation must be less than the danger to life without operation. Therefore, for a "good risk" patient, the risk to life must be minimal and the chance of success maximal. This is especially true when the use of a pump and oxygenator is required and when operation necessitates the opening of the ventricle. Pumps will undoubtedly be improved and necessary precautions better understood. In the meantime, there is no haste for the correction of all malformations and no excuse for developing technique on a "good risk" patient. A patient with a small ventricular septal defect and a low pressure in the pulmonary artery (i. e., 40 mm. Hg or under) is an excellent example. A child with this type of ventricular septal defect will usually have a heart of approximately normal size, a harsh systolic murmur and thrill, a basically normal electrocardiogram, and no undue accentuation of the pulmonary second sound. This malformation is readily compatible with a long and active life; furthermore, there is no evidence that the patient will ever develop pulmonary hypertension. Therefore, children with this type of defect should not undergo surgery until the technique has been so well perfected that the mortality is low and the mortality, combined with the morbidity from the complications of operation, is reduced to a minimum. The fact should be squarely faced that there are today a number of patients who survive open heart surgery but are unimproved by it. The defect is not completely closed, cardiac enlargement has resulted from the ventriculotomy, or the most serious of all complications has occurred, that is, operation has caused a complete heart block. This latter complication has carried a nearly 100% fatality over a five-year period.

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[1] Standards of Care for Patients with Congenital Heart Disease, American Heart Association, Circulation (May 21) 1960, p. 615.

It is quite as much the responsibility of the physician to know when and how long to postpone operation as to know what malformations are operable. My plea is to go slowly and thereby to save life.

HELEN B. TAUSSIG, M.D.
Baltimore, Md.

OCULAR TOXOPLASMOSIS

In Kimura's review of literature on the uveal tract for 1958-1959, he stresses the paucity of articles on uveitis. The Uveitis Symposium, sponsored by the Alfred P. Sloan Foundation, Inc., is probably the year's most important contribution to the subject.[1] It is valuable because almost one-half of the participants were not ophthalmologists but included immunologists, microbiologists, virologists, and rheumatologists. The report is primarily concerned with granulomatous uveitis.

In a study of 100 cases of granulomatous uveitis, Schlaegel found that 82% involved the posterior segment. Skin-test studies demonstrated that 4% of the cases showed ocular flare-up on testing with Old tuberculin; the histoplasmin skin test gave 1% of flare-ups. Toxoplasmin and brucellergen skin tests did not result in a flare-up. Toxoplasma dye tests were positive in 68% and toxoplasmin skin tests in 58%. X-ray examination of the chest was of little value. In Schlaegel's experience, pyrimethamine and sulfadiazine were of little value in treating patients with toxoplasmosis, and toxic depression of the bone marrow was quite frequent. The penicillin therapeutic test and treatment with isoniazid were of definite value. Kimura questions the value of the penicillin therapeutic test, and furthermore he fears that, if this test becomes accepted, penicillin reactions and deaths may result.

Ocular toxoplasmosis appears to play an important part in the pathology of the uveal tract disease. In a study of 36 cases of congenital toxoplasmosis, Hogan found that only 20% of these patients showed evidence of cerebral calcification; 30%, unilateral ocular involvement; 33%, late relapses of congenital infection; and 55%, strabismus. He reemphasized the importance of the latter sign. In the diagnostic tests he found that 9 of these 36 patients had positive methylene blue dye tests and negative toxoplasmin skin tests. Hogan stressed that ocular inflammation rarely occurred during the course of postnatally acquired systemic toxoplasmosis. He emphasized the importance of biopsies of large lymph nodes, in cases of uveitis, for both microscopic and cultural studies.

Hogan, Zweigart, and Lewis reported on the recovery of Toxoplasma organisms from an eye with chronic posterior uveitis. The patient had had a quiescent disease up to the age of 12 years, the chlorioretinal lesions being discovered at the age of 1½ years. At 12 years of age there was a sudden diminution of vision in his good eye. At the age of 20 years the eye was removed for cosmetic reasons, and on culture the parasite was isolated. This is an important report. It demonstrates the long persistence of organisms in pseudocysts formed in tissues.

Remington, Jacobs, and Kaufman studied chronic toxoplasmosis in rats and found only occasional transmission of parasites from chronically infected mothers to their offspring. They found that the uterus of rats may contain latent parasites. From a statistical standpoint, they concluded that the obstetrician and pediatrician can still offer to an afflicted child's parents the encouragement that their chances of having a normal child later are good.

Investigations in England and Australia suggest that Toxoplasma has a wide geographical distribution in a wide host range. However, Toxoplasma rarely causes apparent harm. We do not know of any natural means of transmission in man, except the congenital, which accounts for only very few cases. Lunde and Jacobs believe that the hemagglutination test has the advantage over the methylene blue dye test in that it is easier to perform, safer, and the antigen can be standardized.

In the treatment of ocular toxoplasmosis, pyrimethamine and the sulfonamides seem to be the only drugs that may be useful. Hogan, Zweigart, and Lewis found in experiments on mice that neither sulfadiazine nor a combination of sulfadiazine with pyrimethamine was effective in preventing a chronic toxoplasmic infection of the eye and brain after inoculation of the organisms into the vitreous. Vaccination of human volunteers with whole heat-killed Toxoplasma resulted in the production of significant levels of dye test antibodies. This study is important because the obvious treatment of congenital toxoplasmosis is its prevention. At the present, the immunization of uninfected pregnant women may be the very method of control.

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[1] Uveitis Symposium, Council for Research in Glaucoma and Allied Diseases, Survey Ophth. 4:June (pt. 2) 1959.

GOVERNMENT SERVICES

DEPARTMENT OF DEFENSE

Dr. Hoogstraal Honored.—The Department of Defense Distinguished Civilian Service Award, highest honor conferred on civilian employees by the Department of Defense, was presented to Dr. Harry Hoogstraal, head of the department of medical zoology, Naval Medical Research Unit no. 3, Cairo, United Arab Republic, for his research on ticks and tick-borne diseases of man and animals. His work is of major significance not only to military medicine but to the welfare of all the peoples of regions where tick-borne diseases are a serious health problem.

ARMY

Disaster Training Programs.—Three officers from the surgeon general's office participated in a series of training programs on medical aspects of health mobilization offered by the Public Health Service's division of health mobilization. The first course was held in April in Brooklyn, N. Y., the second in May in Battle Creek, Mich., and the third in June in Alameda, Calif. These courses provided up-to-date disaster information and training to a nucleus of professional personnel concerned with medical and health needs of the civilian population during natural or man-made disasters. The officers representing the Army were Col. Albert J. Glass, M. C., chief, psychiatry consultant to the Army surgeon general; Lieut. Col. Robert E. Van Gilder, M. S. C., chief, training doctrine branch, personnel and training division; and Lieut. Col. William W. Southard, M. S. C., chief, matériel control branch, supply division.

Selected specialists from all over the United States, including representatives of the American Medical Association and the medical services of the Armed Forces, participated in the programs. The Army medical service presented an exhibit on first aid and self-aid and another on Army medical service training aids that showed current training mediums developed in support of the Army's emergency medical care program.

NAVY

Personal.—Rear Adm. Cecil D. Riggs assumed the duties of fleet medical officer for the U. S. Pacific Command headquarters in Pearl Harbor in May. He relieved Rear Adm. Courtney G. Clegg, who was assigned as medical officer for the Ninth Naval District, with headquarters in the Great Lakes Naval Training Station in Illinois. Admiral Riggs' previous assignment was that of commanding officer of the U. S. Naval Hospital, Chelsea, Mass.

Retirements.—The following Navy Medical Corps officers were retired from the U. S. Navy, effective May 1: Capt. A. C. Abernathy after more than 29 years of active service. He was last assigned as commanding officer of the U. S. Naval Hospital, Jacksonville, Fla.—Capt. C. F. Gell after more than 22 years of active service. He was last assigned in the Office of Naval Research, Department of the Navy, Washington, D. C.—Capt. J. V. Land after more than 29 years of active service. His last assignment was as commanding officer, U. S. Naval Hospital, Pensacola, Fla.—Capt. S. M. Smith after more than 20 years of active service. He was last assigned as district medical officer, Ninth Naval District, Great Lakes, Ill.

VETERANS ADMINISTRATION

Personal.—Dr. Ralph S. Metheny, manager of the Veterans Administration Hospital, Boston, has been named area medical director for the VA in St. Paul, Minn., effective Aug. 1. He will succeed Dr. Oreon K. Timm, who will be transferred to the VA's central office in Washington, D. C.—Dr. Hardy A. Kemp, director of professional services at the Veterans Administration Hospital, Portland, Ore., since April, 1958, has been appointed manager of the VA hospital, Atlanta, Ga.—Dr. H. Martin Engle, manager of the Veterans Administration Hospital in Denver, Colo., was appointed deputy chief medical director for the VA in Washington, D. C. He succeeds Dr. Roy A. Wolford, who retired at the end of April after more than 40 years of federal service.

NATIONAL SCIENCE FOUNDATION

Postdoctoral Fellowships in Science.—The Department of State and the National Science Foundation have awarded 41 North Atlantic Treaty Organization (NATO) postdoctoral fellowships in science. These awards will enable United States fellows to study in 10 foreign nations, while outstanding foreign scientists from other NATO countries will come to the United States for further training. The fellows will receive a basic 12-month stipend of $4,500. In addition, limited round-trip travel and dependency allowances are provided. Awards in the medical sciences went to James P. Buell of California, who will study at the Equine Research Station in England; David P. Hall of Georgia, who will go to the Karolinska Institute in Sweden; and Robert L. Spears of California, who will study at the University of Paris.

DEATHS

Adams, Charles Ross, Atlanta, Ga.; Emory University School of Medicine, Atlanta, 1918; served as commissioner of Fulton County; died in Halifax District Hospital, Daytona Beach, Fla., April 20, aged 65, of coronary occlusion and diabetes mellitus.

Baird, Robert L. Ⓜ Dixon, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1908; fellow of the American College of Surgeons; member of the Industrial Medical Association; associated with the Dixon Public Hospital; died March 25, aged 76, of coronary occlusion.

Biedermann, Jacob Ⓜ Austin, Minn.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1904; died in Minneapolis March 1, aged 84, of cerebrovascular accident.

Blanchard, Lafayette Wendell, Branson, Mo.; Cotner University Medical Department, Lincoln, Neb., 1894; died April 11, aged 94, of carcinoma of the prostate.

Boehringer, William Gottlob, Prospectville, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1907; veteran of World War I; died April 6, aged 73, of coronary occlusion.

Bouyer, Harsba Fleminster Ⓜ Chicago; Meharry Medical College, Nashville, Tenn., 1928; veteran of World War II; associated with the Provident Hospital; died in the Veterans Administration Westside Hospital April 11, aged 65, of uremia and chronic pyelonephritis.

Brown, Harry Lee Ⓜ Commander, U. S. Navy, retired, Buffalo, N. Y.; Columbian University Medical Department, Washington, D. C., 1901; commissioned in the medical corps of the U. S. Navy in 1904 and retired Sept. 1, 1933; veteran of World War I; during World War II senior medical officer attached to the Recruiting Office in Buffalo; died April 21, aged 85, of coronary thrombosis.

Buckley, Robert, Kecoughtan, Va.; Medical College of Virginia, Richmond, 1933; veteran of World War II and among other citations was awarded the Bronze Star; served as medical director for the Virginia State Penitentiary in Richmond; on the staff of the Veterans Administration Center; died April 25, aged 52, of acute myocardial infarction.

Buford, Charles Conrad, Trenton, N. J.; Meharry Medical College, Nashville, Tenn., 1916; died in the Veterans Administration Hospital, East Orange, March 20, aged 69, of cerebral thrombosis.

Buist, Archibald Johnston Jr., Charleston, S. C.; Medical College of South Carolina, Charleston, 1930; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; associate professor of surgery at his alma mater; veteran of World War II; for many years chairman of the board of commissioners of Roper Hospital, where he died April 22, aged 54, of bronchogenic carcinoma.

Cary, Erwin Charles Ⓜ Reedsville, Wis.; born Feb. 26, 1884; Milwaukee Medical College, 1910; member of the American Academy of General Practice; served as secretary of the Manitowoc County Medical Society and as president of the Manitowoc County Health Officers' Association; formerly president of the Marquette University Medical Alumni Association; veteran of World War I; health officer for the village of Reedsville and also for the towns of Rockland and Franklin; associated with the Two Rivers (Wis.) Municipal Hospital, the Memorial Hospital, and the Holy Family Hospital in Manitowoc, where he died April 23, aged 76, of diabetes mellitus and cerebral thrombosis.

Cavenee, Ebbert Lamonte, Champaign, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1913; veteran of World War I; died in the Veterans Administration Hospital, Hines, March 28, aged 77.

Cawley, Bernard M., Greeley, Colo.; Barnes Medical College, St. Louis, 1899; died April 21, aged 93, of carcinoma of the bladder.

Clark, Morris Holden, Trinidad, Colo.; Columbia University College of Physicians and Surgeons, New York City, 1913; specialist certified by the American Board of Ophthalmology; served on the staff of the St. Mary–Corwin Hospital in Pueblo; died in the Colorado State Hospital, Pueblo, April 15, aged 72, of adenocarcinoma of the prostate.

Colleran, Harold Leo Ⓜ Peckville, Pa.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1938; served as a director of the First National Bank of Jessup; associated with St. Joseph's Hospital, Carbondale, Mid Valley Hospital, Peckville, St. Mary's Hospital, Scranton State Hospital, and Mercy Hospital, Scranton, where he died April 1, aged 46, of pneumonia.

Coppedge, Oscar S., Depew, Okla.; Barnes Medical College, St. Louis, 1905; served as president of the Creek County Medical Society; member of the board of directors of the Depew State Bank, which

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Ⓜ Indicates Member of the American Medical Association.

he helped organize; member of the city commission and school board; died in the Bartlett Memorial Hospital, Sapulpa, March 25, aged 78.

Coryell, Schofield Michael, Cleveland, Ohio; Eclectic Medical College, *Cincinnati, 1919; member of the Industrial Medical Association; veteran of* World War I; served on the Selective Service Board during World War II; associated with St. Alexis Hospital, where he died April 21, *aged 66, of acute* myocardial infarction.

Cosco, Nicholas Philip Ⓜ Middletown, N. Y.; born in Middletown Feb. 15, 1910; Syracuse University College of Medicine, 1934; member of the American Academy of General Practice; for many years city health officer; an associate member of the attending staff at Elizabeth A. Horton Memorial Hospital in Middletown and St. Luke's Hospital in New York City; consultant in medicine at St. Anthony's Hospital in Warwick and at the Middletown State Homeopathic Hospital; *recently cited by the Middletown Junior Chamber of Commerce for his work in administering Salk poliomyelitis vaccine and a similar award was made last year by the National* Foundation; died in the Columbia Presbyterian Medical Center, New *York City, March 28, aged 50,* of cardiorenal failure.

Courtney, Harold Ⓜ Syracuse, N. Y.; born in Syracuse, May 19, 1900; *Syracuse University College of* Medicine, 1925; specialist certified by the American Board of Proctology; fellow of the International College of Surgeons, Pennsylvania Proctologic Society, and the American Proctologic Society, which gave him its annual Hermance Award in 1946 and *again in 1949 for original research and advancement* of the proctologic field; honorary fellow of the Brazilian Proctologic Society, Rio de Janeiro, and the Brazilian Congress of Proctology, Rio de Janeiro; member of the Syracuse Academy of Medicine; on the staffs of the General Hospital and the Onondaga Sanatorium; died in the Hospital of the Good Shepherd April 13, aged 59, of spinal atrophy.

Cowell, Selden Sylvester Ⓜ *Carlisle, Pa.;* Hahnemann Medical College and Hospital of Philadelphia, 1909; served on the staff of the Carlisle Hospital, where he died April 23, aged 73, of myocardial infarction.

Crane, Jay Freeman Ⓜ Los Angeles; born in Lead, S. D., Oct. 1, 1916; University of Southern California School of Medicine, Los Angeles, 1942; interned at the Los Angeles County Hospital, where he served a residency; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the International College of Surgeons and the American College of Surgeons; president-elect of the University of Southern California Medical Alumni Association; veteran of World War II; served on the faculty of his alma mater; associated with the Queen of Angels Hospital, St. Vincent's Hospital, Los Angeles County *Hospital, and the Hospital of the* Good Samaritan, where he died April 20, aged 43 of acute myocardial infarction.

Craven, Howard Thomas, *Washington, D. C.; Indiana University School* of Medicine, Indianapolis 1944; interned at *the* Staten Island Hospital in Staten Island, N. Y.; served a residency at the Brooklyn Cancer Institute in Brooklyn, and the *Methodist Hospital in Indianapolis; formerly an* officer in the U. S. Air Force Reserve; died in Fort Wayne, Ind., April 27, *aged 39.*

Cunningham, Arthur Franklin, Spokane, Wash. *Rush Medical College, Chicago, 1931; fellow of the* American College of Surgeons; associated with Sacred Heart Hospital, Deaconess Hospital, and the St. Luke's Hospital, where he died April 11 aged 55, of brain tumor.

Dahl, John Julian Ⓜ La Grange, Ill.; Northwestern *University Medical School, Chicago, 1941;* veteran *of World War II; for many years on the* staff of *St. Anne's Hospital in Chicago;* associated with *the Community Memorial General Hospital,* where *he died April 14, aged 44, of infectious* hepatitis.

Devine, John Leo Sr., Minot, *N. D.;* University of Minnesota College of Medicine and Surgery, Minneapolis, 1904; at one time city health officer; during World War II served on the Selective Service Board and received a congressional citation for his service; associated with *St. Joseph's* Hospital; died April 1, aged 79, of thrombosis *of* the right carotid artery.

Donovan, Florence Timothy, Wilton, Conn.; Cornell University Medical College, New York City, 1911; fellow of the American College of Surgeons; served as director of surgery and president of the medical board of Staten Island (N. Y.) Hospital; associated with Richmond Memorial and Sea View hospitals in Staten Island, N. Y.; died April 24, aged 74, of cerebral vascular accident.

Donovan, Robert Richard, Brooklyn; Loyola University School of Medicine, *Chicago,* 1930; died March 27, aged 58, of viral pneumonia and paralysis agitans.

Donovan, Thomas Magner, Gardner, Mass.; Tufts College Medical School, Boston, 1946; interned at the Burbank Hospital in Fitchburg; member of the *American* Academy of General Practice; formerly an officer in the medical corps, Army of the United States; certified by the National Board of Medical Examiners; associated with the Gardner State Hospital; died in Worcester April 23, aged 38, of pneumonia.

Dordick, Jacob Russell Ⓜ New *York City;* New York University College of Medicine, 1936; specialist certified by the American Board of Internal Medicine; member of the American Rheumatism ssociation; associated with the Beth Israel Hos-ital, where he served an internship, and where he ied April 22, aged 47, of arteriosclerotic heart isease.

ougall, John Park Ⓜ Los Angeles; California ledical College, San Francisco, 1904; past-presi-ent of the state board medical examiners; asso-iated with the French Hospital, Hospital of the ood Samaritan, and the California Hospital; died arch 31, aged 85, of arteriosclerotic heart disease.

ougherty, William Byrne Ⓜ Chicago; College of hysicians and Surgeons of Chicago, School of ledicine of the University of Illinois, 1906; for any years supervisor for the board of health; erved on the staff of Augustana Hospital, where e died April 16, aged 81, of arteriosclerotic heart isease.

ownes, Clarence Eugene, Bradenton, Fla.; Jeffer-on Medical College of Philadelphia, 1888; died pril 23, aged 94, of coronary disease.

u Boise, Otho Kavanaugh Ⓜ Lockhart, Texas; ulane University of Louisiana School of Medicine, ew Orleans, 1935; member of the American Acad-my of General Practice; veteran of World War II; ied in the Lockhart Hospital Jan. 10, aged 49, of oronary occlusion.

ubois, Morris George Ⓜ Los Angeles; Fordham niversity School of Medicine, New York City, 921; died March 18, aged 68, of coronary disease.

udley, Harlan, Findlay, Ohio; Johns Hopkins Uni-ersity School of Medicine, Baltimore, 1903; from 939 to 1945 served on the staff of the Allen Me-orial Hospital, Oberlin; died in the Blanchard alley Hospital March 28, aged 88, of coronary isease.

uff, Roden Robinson Jr. Ⓜ Chicago; Creighton niversity School of Medicine, Omaha, 1936; in-erned at St. Luke's Hospital; member of the Indus-rial Medical Association; formerly associated with t. Luke's and Alexian Brothers hospitals; died in ittle Company of Mary Hospital April 15, aged 53, of duodenal ulcer with hemorrhage.

Edwards, Jesse Clifton, Berkeley, Calif.; Ohio State University College of Medicine, Columbus, 1915; veteran of World War I; died in the Alta Bates Hospital March 28, aged 72, of arteriosclerotic heart disease.

Ehrenreich, Samuel George, New York City; Columbia University College of Physicians and Surgeons, New York City, 1909; died in the Lenox Hill Hospital April 3, aged 73, of carcinoma of the stomach.

Elson, Veryl J. Ⓜ Paola, Kan.; University of Kansas School of Medicine, Kansas City, 1935; interned at St. Mary's Hospital in East St. Louis, Ill.; veteran of World War II; for many years a member of the board of education; associated with the Miami County Hospital; died April 5, aged 53, of myocardial infarction.

Englebert, William Frederick Jr., Tuscaloosa, Ala.; University of Louisville (Ky.) School of Medicine, 1931; veteran of World War II; for many years associated with the Bryce Hospital; died in the Veteran Administration Hospital April 12, aged 54, of coronary occlusion.

Falk, Louis Aaron, Brooklyn; University and Bellevue Hospital Medical College, New York City, 1912; died in the Kingshighway Hospital April 12, aged 71, of anuria.

Fidelman, Norman Edward Ⓜ Foley, Minn.; University of Minnesota Medical School, Minneapolis, 1948; interned at the Milwaukee County Hospital in Milwaukee; formerly an officer in the medical corps of the U. S. Army Reserve; president of the Central Minnesota Chapter of the American Academy of General Practice; associated with St. Cloud (Minn.) Hospital, where he died April 22, aged 35, of a heart attack.

Fink, Marion Shelley Ⓜ Elmhurst, Ill.; University of Illinois College of Medicine, Chicago, 1916; veteran of World War I; on the staff of the West Suburban Hospital in Oak Park, Ill.; died March 12, aged 73, of pulmonary embolism.

Finney, Royal Houghtelin Ⓜ Pueblo, Colo.; Harvard Medical School, Boston, 1910; for many years associated with St. Mary–Corwin Hospital, where he died April 18, aged 76, of multiple myeloma.

Fisher, George John, Madison, N. J.; born in Cincinnati April 2, 1871; Cincinnati College of Medicine and Surgery, 1898; national scout commissioner of the Boy Scouts of America; received a Silver Buffalo Award in 1926 "for distinguished service to boys," Luther Halsey Gulick medal "for distinguished service in physical education" in 1929, Silver Tamaraw by National Council Boy Scouts of Philippines in 1950, and award of Fisher Body Craftsman Guild in 1956; in 1951 received the honorary doctor of science from Springfield (Mass.) College; editor of many physical education and scouting publications; died April 20, aged 89, of cerebral arteriosclerosis.

Fitch, Ella, Harlan, Iowa; Woman's Medical College, Chicago, 1884; died April 6, aged 96, of carcinoma of the breast.

Fleming, Leroy Newton, Palos Verdes Estates, Calif.; Johns Hopkins University School of Medicine, Baltimore, 1914; for many years practiced in Detroit, where he was on the staffs of the Harper and Grace hospitals; died April 3, aged 72.

Fox, Paul Christopher Ⓜ Coral Gables, Fla.; Rush Medical College, Chicago, 1912; formerly on the faculty of his alma mater; specialist certified by the American Board of Obstetrics and Gynecology;

member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; formerly practiced in Oak Park, Ill., where he was associated with the West Suburban Hospital; died May 8, aged 74.

Frank, Adolph Mitchell Ⓜ St. Louis; University of Illinois College of Medicine, Chicago, 1913; for many years on the staff of the Lutheran Hospital; died April 20, aged 70, of heart disease.

Freel, John Aloysius Ⓜ Bay City, Mich.; Marquette University School of Medicine, Milwaukee, 1934; member of the American Academy of General Practice; associated with General and Mercy hospitals; died April 20, aged 54, of cerebral hemorrhage.

Friedmann, Otto Fleisher, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1910; died Jan. 7, aged 81, of arteriosclerotic cardiovascular disease.

Gammon, John Henry, Knoxville, Tenn.; Lincoln Memorial University Medical Department, Knoxville, 1912; also a pharmacist and lawyer; served as a member of the Tennessee House of Representatives and as state senator; member of the school board of Knox County; at one time postmaster at Briceville and Coal Creek; formerly associated with the Eastern State Hospital, Baptist Hospital, University of Tennessee Hospital, and the Fort Sanders Presbyterian Hospital, where he died April 17, aged 81, of chronic lymphatic leukemia.

Garman, Harry Franklin Ⓜ Barnesboro, Pa.; University of Pittsburgh School of Medicine, 1914; veteran of World War I; chief surgeon on the staff of the Miners' Hospital of Northern Cambria in Spangler; chairman of the board of directors of the Farmers' and Merchants' Bank in Cherry Tree; died April 21, aged 72, of cerebral thrombosis.

Getze, George Wilbur Ⓜ Carlsbad, Calif.; Hahnemann Medical College and Hospital of Philadelphia, 1906; veteran of World War I; died in Veterans Administration Hospital in Long Beach April 6, aged 76, of bronchopneumonia.

Gray, Albert Stanley Ⓜ West Hartford, Conn.; born in London, England, in 1881; University and Bellevue Hospital Medical College, New York City, 1915; specialist certified by the American Board of Preventive Medicine; health director of West Hartford; formerly deputy commissioner of the Connecticut State Department of Health and for many years director of its Bureau of Industrial Hygiene; served as associate professor of public health at Yale University in New Haven; for his pioneering work in the prevention of occupational illness in the state, received in 1948 a citation from the Connecticut Safety Society; the first chairman of the industrial hygiene section of the American Public Health Association and a past-president of the American Conference of Governmental Industrial Hygienists; served in the U. S. Public Health Service; died in St. Francis Hospital, Hartford, April 21, aged 79, of granulocytic leukemia and left lower lobe pneumonia.

Gray, Joel Boyd, New Orleans; Tulane University School of Medicine, New Orleans, 1932; member of the American Academy of General Practice; charter director and past-president of Louisiana Academy of General Practice; president of the Jefferson Reserve Life Insurance Company; charter director of Goodwill Industries of New Orleans; on the staff of the Southern Baptist Hospital; died April 6, aged 54, of dissecting aneurysm of the aorta.

Graybiel, George Proudfoot Ⓜ Caledonia, Mich.; University of Michigan Medical School, Ann Arbor, 1925; served on the staff of the Blodgett Memorial Hospital, Grand Rapids, where he died April 21, aged 67, of coronary occlusion.

Griffith, Wayne, Chester, Vt.; University of Vermont College of Medicine, Burlington, 1933; served as a member of the Vermont State Health Commission; past-president of the Vermont State Medical Society; member of the American Academy of General Practice; health officer; associated with the Springfield (Vt.) Hospital, where he died April 20, aged 53, of cancer.

Hall, Forest Frank, Dunedin, Fla.; Jefferson Medical College of Philadelphia, 1909; died in the Hamilton County Hospital, Webster City, Iowa, Feb. 13, aged 78, of adenocarcinoma of the nasopharynx.

Hardenstein, Frank H., New Orleans; Hahnemann Medical College and Hospital of Philadelphia, 1908; member of the staff of the Southern Baptist Hospital; died April 21, aged 77, of coronary thrombosis.

Herr, Albert Hiram, Lima, Ohio; Starling Medical College, Columbus, 1903; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; veteran of World Wars I and II; died in the Lima Memorial Hospital April 15, aged 81.

Herrlin, John Samuel Oliver Jr. Ⓜ New York City; born in New York City Aug. 10, 1897; New York Medical College and Flower Hospital in New York City, 1923; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; professor of clinical surgery at his alma mater; associated with the Southampton (N. Y.) Hospital, Bird S. Coler Memorial Hospital and Home, Flower and Fifth Avenue Hospitals, and the Metropolitan Hospital; surgical consultant to Consolidated Edison Company of New York; died in Great Neck, N. Y., May 1, aged 62, of massive cerebral hemorrhage.

Hill, Walter Herbert, Fredericksburg, Texas; University of Texas School of Medicine, Galveston, 1922; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past-president of the Bexar County Medical Society; veteran of World War II; served on the staffs of the Robert B. Green Memorial and Nix Memorial hospitals in San Antonio; associated with the Keidel Memorial Hospital; died in San Antonio April 12, aged 63, of coronary occlusion.

Hitchcock, Waldo Philip Ⓜ Columbia, Mo.; Medical College of Alabama, Birmingham, 1949; interned at the Jefferson–Hillman Hospital in Birmingham, Ala., where he served a residency; associate professor of anesthesiology at the University of Missouri School of Medicine; served on the faculty of his alma mater and the Hahnemann Medical College and Hospital of Philadelphia; specialist certified by the American Board of Anesthesiology; member of the American Society of Anesthesiologists, Missouri Society of Anesthesiologists, Southern Society of Anesthesiologists, International Anesthesia Research Society, American Society for Pharmacology and Experimental Therapeutics, Sigma X, Alpha Omega Alpha, and Phi Chi; anesthesiologist, University of Missouri Teaching Hospital; died April 17, aged 43, of coronary arteriosclerosis.

Honeycutt, Charles Fletcher, Missoula, Mont.; Johns Hopkins University School of Medicine, Baltimore, 1935; fellow of the International College of Surgeons, of which he was a vice-regent, and the American College of Surgeons; interned at the George F. Geisinger Memorial Hospital in Danville, Pa.; veteran of World War II; on the staff of the St. Patrick Hospital; died April 13, aged 50, of pneumonia.

Howd, Helmer Powers, Troy, N. Y.; Harvard Medical School, Boston, 1928; certified by the National Board of Medical Examiners; veteran of World War II; industrial physician for Cluett, Peabody & Company; on the staffs of the Leonard and Samaritan hospitals; died April 16, aged 58, of coronary arteriosclerosis.

Huebel, Rudolph, New York City; Universita Karlova Fakulta Lekarska, Praha, Austria, 1915; died in the Montefiore Hospital Feb. 28, aged 71, of leukemia.

Hunter, Erman Floyd Ⓜ New Concord, Ohio; Western Reserve University School of Medicine, Cleveland, 1919; died in the Bethesda Hospital, Zanesville, April 15, aged 69, of myocardial infarction.

Hunter, Walter Benjamin, Coushatta, La.; Memphis (Tenn.) Hospital Medical College, 1909; served as president of the Red River Parish Medical Society and the Fourth District Medical Society; veteran of World War I; died in the Veterans Administration Hospital, Shreveport, April 12, aged 78, of a heart attack.

Johnson, Arnold D. Ⓜ Seattle; College of Medical Evangelists, Loma Linda and Los Angeles, 1931; died April 14, aged 62, of coronary thrombosis.

Johnson, Dexter Dean, Belmont, Miss.; University of Tennessee College of Medicine, Memphis, 1914; died in the North Mississippi Community Hospital, Tupelo, April 12, aged 70, of coronary thrombosis.

Johnson, Harold Henry, Esparto, Calif.; Tufts College Medical School, Boston, 1919; died April 17, aged 65, of arteriosclerotic heart disease.

Jones, Horace Croom Ⓜ Grand Rapids, Mich.; University of Arkansas School of Medicine, Little Rock, 1928; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; past-president of the Detroit Roentgen Ray Society; veteran of World War II; since 1946 chief of x-ray department of Blodgett Memorial Hospital, where he died April 20, aged 61, of uremia.

Kelso, Raymond William Ⓜ Long Beach, Calif.; University of Illinois College of Medicine, Chicago, 1927; veteran of World War II; on the teaching staff, Harbor General Hospital, Torrance; on the staffs of Long Beach Community and St. Mary's hospitals, and the Seaside Memorial Hospital, where he died April 19, aged 63, of carcinoma of the sigmoid.

Knolle, Waldo Austin Ⓜ Brenham, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1917; past-president of the Washington County Medical Society; chief of staff, Sarah B. Milroy Memorial Hospital; veteran of World War I; died April 18, aged 66, of coronary occlusion.

Lawrence, Wilbert Wight, Arcadia, Calif.; Western Reserve University School of Medicine, Cleveland, 1915; formerly practiced in Norwalk, Ohio, where he was health officer, associated with the Norwalk Community Hospital, and past-president of the Kiwanis Club; died April 11, aged 76, of congestive heart failure.

Lewis, Dorsey Waitman, Middletown, Del.; University of Maryland School of Medicine, Baltimore, 1896; past-president of the Medical Society of Delaware; past-president of the New Castle County Medical Society; member of the board of directors of Delaware Trust Company; surgeon for the Pennsylvania Railroad; on the staff of the Delaware Hospital in Wilmington and trustee of the Delaware State Hospital in Farnhurst; died April 19, aged 86, of heart disease.

Lindquist, John A. Ⓜ Springfield, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1901; served as city health officer; formerly city and county physician; on the staff of the Memorial and St. John's hospitals; died in the Memorial Hospital April 15, aged 87.

Lipnitzky, Samuel Jacob Ⓜ Lincoln, Ill.; born in Kiev, Russia, July 17, 1903; University of Illinois College of Medicine, Chicago, 1934; interned at the Jackson Park Hospital in Chicago; served as a member of the Illinois Department of Public Welfare; fellow of the American Psychiatric Association, American Association on Mental Deficiency, American Medical Writers Association, and the American Association for the Advancement of Science; formerly associated with the Dixon (Ill.) State Hospital and the Mansfield State Training School and Hospital in Mansfield Depot, Conn.; on the staff of the Lincoln State School, where he died April 13, aged 56, of cerebral hemorrhage.

McCarthy, Elmer Vincent, Chicago; St. Louis College of Physicians and Surgeons, 1923; past-president of the South Chicago branch of the Chicago Medical Society; associated with the South Shore Hospital, where he died May 1, aged 66, of cerebral infarction.

MacMillan, John Miller, Rochester, N. Y.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1931; past-president of the Rochester Pathological Society; in 1950 appointed medical superintendent of the Iola–Monroe County Tuberculosis Sanatorium; associated with the Rochester General Hospital, Highland Hospital, and the Monroe County Infirmary; died April 14, aged 55, of duodenal ulcer with massive hemorrhages.

Mainer, Raymond George Ⓜ New Britain, Conn.; born in New Britain, Conn., Nov. 6, 1913; University of Vermont College of Medicine, Burlington, 1939; interned at the New Britain General Hospital, where he served a residency; served a residency at the New York Post-Graduate Medical School and Hospital in New York City; director of the Hartford County Medical Society; specialist certified by the American Board of Surgery; certified by the National Board of Medical Examiners; veteran of World War II; past-president of the Kiwanis Club; associated with the New Britain General Hospital, where he died April 14, aged 46, of cancer.

Marks, Morris Hyman, Detroit; University of Michigan Medical School, Ann Arbor, 1924; member of the Industrial Medical Association; on the staff of Sinai Hospital, died in the Mount Carmel Mercy Hospital April 17, aged 59, of a heart attack.

Masland, Harvey Christian Ⓜ Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1891; died in the Pennsylvania Hospital April 18, aged 90, of acute myocardial infarction.

Thurston, Eric Washington Ⓜ La Jolla, Calif.; St. Louis University School of Medicine, 1929; specialist certified by the American Board of Pathology; member of the College of American Pathologists and the American Society of Clinical Pathologists; veteran of World War II; died April 9, aged 56.

Traxler, Felix John Ⓜ Henderson, Minn.; John A. Creighton Medical College, Omaha, 1915; veteran of World War I; past-president of the Nicollet, Le Sueur Counties Medical Society; health officer; served as a member of the school board; associated with the Arlington (Minn.) Municipal Hospital; died in St. Joseph's Hospital, St. Paul, April 11, aged 69, of coronary disease.

Volberding, Harry Henry Ⓜ Roselle, Ill.; University of Illinois College of Medicine, Chicago, 1915; associated with the St. Joseph Hospital in Elgin and the Memorial Hospital of Dupage County in Elmhurst; died in Bensenville April 21, aged 69, of congestive heart failure.

Waldman, David Paul Ⓜ New York City; Long Island College Hospital, Brooklyn, 1904; died in the Park East Hospital April 12, aged 77, of coronary occlusion.

Warden, Herbert Gerald, New York City; Boston University School of Medicine, 1928; certified by the National Board of Medical Examiners; died Feb. 8, aged 63, of coronary thrombosis.

Weddle, Charles, Dinuba, Calif.; Northwestern University Medical School, Chicago, 1904; died in the Alta District Hospital April 4, aged 85, of generalized arteriosclerosis.

Weinstein, Jacob Ⓜ Brooklyn; L. R. C. P., Edinburgh, L. R. C. S., Edinburgh, L. R. F. P., Edinburgh and L. R. F. P. & S., of Glasgow, Scotland, 1936; on the staff of the Unity Hospital, where he died Feb. 19, aged 50, of acute myocardial infarction.

Whitney, Chester F. S., Croton-on-Hudson, N. Y.; University and Bellevue Hospital Medical College, New York City, 1899; veteran of World War I; in 1924 the French government awarded him its gold medal of honor; served for forty years in the medical department of the Home Life Insurance Company, retiring as its director in 1940; a founder, for many years director, and past-president of the New York University Alumni Federation; in 1932 received the New York University Alumni Meritorious Service Medal and in 1958 the university's presidential citation; died in the Doctors Hospital, New York City, April 13, aged 84, of postoperative hemorrhage, retroperitoneal.

FOREIGN LETTERS

BRAZIL

Cancer of the Lung.—Dr. Bindo Guida presented to the Associação Paulista de Medicina a report on the surgical treatment of 62 of a series of 230 patients with cancer of the lung. The resection of the diseased lung was possible in 26 patients; in one patient, as a palliative measure, a lower lobectomy was performed; and in the remaining 35 patients the chest was opened and then closed because local conditions contraindicated pulmonary resection. Seven of the 27 patients who received adequate surgical treatment and 3 of the other 35 had operative deaths. Among the patients who did not die during the operation and the postoperative period were 12 who died in the next 24 months. Only 2 of these 12 patients survived for more than a year. The author preferred pneumectomy but stated that the results of the surgical treatment of primary cancer of the lung were not encouraging, although it is the best treatment that we have. Thoracotomy increased the suffering of the patients in the postoperative period and shortened the lives of some patients. The author emphasized the necessity for exercising a great care in the selection of the patients for operation and the need to search for signs contraindicating resection.

CANADA

Promethazine as Local Anesthetic.—The effect of 6 commonly used anesthetics was compared with that of 11 antihistaminic drugs. The margin of safety, expressed in the therapeutic index, was highest with promethazine, which in this experimental setting surpassed the analgesic effect of procaine hydrochloride over 20 times, when used as a subcutaneous injection. Kalz and Fekete (*Canad. M. A. J.* 82:833, 1960) investigated the properties of this preparation more closely. In seven human volunteers the onset, degree, and duration of local anesthesia produced by subcutaneous injections of procaine and of promethazine were compared. Identical results were observed in all patients. It was found that the anesthetic effect of a 2.5% promethazine solution roughly equaled that of a 1% procaine solution. Weaker concentrations tended to induce analgesia more slowly. In addition, promethazine was injected subcutaneously in concentrations ranging from 1.25 to 2.5% and in amounts of 0.5 to 2.0 ml. in 30 patients undergoing minor operations. Satisfactory anesthesia was obtained in all patients when a 2.5% solution was used. Patients sensitive to procaine tolerated promethazine well, and no untoward local or general reactions were seen in this series. Promethazine should not be used for intradermal injections. Concentrations of 2.5% given intradermally cause marked tissue reaction and necrosis. No amounts larger than 2 ml. were given in this series. A general sedative effect should be anticipated with a larger dosage. The authors concluded that promethazine is a powerful local anesthetic, suitable particularly for patients with known or suspected sensitivity to drugs of the procaine group and for patients with a history of intolerance to multiple drugs. Injections must be given subcutaneously, not intradermally.

Heparin Antagonist.—Hexadimethrine bromide was used as a heparin antagonist in six exchange transfusions in infants. Valentine (*Canad. M. A. J.*, page 723, 1960) reported that, while he believes a heparin antagonist is not necessary routine in an exchange transfusion with heparinized blood, hexadimethrine is a safe and effective heparin antagonist for such use in neonates. Coagulation times were determined at the commencement of the exchange transfusion, at the conclusion, and five minutes after the measured dose of hexadimethrine was given. In accordance with the manufacturer's suggestions, 1 mg. of hexadimethrine was used for every 100 I. U. of heparin given. These infants had all received 2,000 I. U. of heparin, but no change in their condition was observed during the injection. Coagulation time was greatly reduced in all patients after administration of hexadimethrine.

DENMARK

Ventricular Septal Defects.—The original Damman-Muller operation for ventricular septal defects in children consisted of segmental excision of the pulmonary artery which was supplemented by application of a polyethylene band around the narrowed portion, but the operation involved the risk that the stenosis might gradually become relatively too narrow. F. Therkelsen and co-workers (*Acta chir. scandinav.* [supp.] 245:249-258, 1959) modified the technique by excising a segment of the pulmonary artery but not applying a band around the narrowed portion. To reduce further the high mortality, they later applied a band around the pulmonary artery and tightened it until a suitable pressure gradient was obtained. These operations were used as a palliative measure in infants with markedly increased pressure in the pulmonary artery after conservative treatment had failed. In a

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The items in these letters are contributed by regular correspondents in the various foreign countries.

series of 22 infants operated on there were 10 operative deaths, but among the last 10 patients operated on only 3 operative deaths occurred. Of nine patients who were followed up for six months to four years, seven showed excellent or good results. The authors concluded that after the lapse of a few years, the palliative operation presumably must be followed by an open cardiotomy.

Coarctation of the Aorta in Infants.—Coarctation of the aorta was diagnosed in 20 of 266 infants with severe congenital heart disease seen at the Queen Louise Children's Hospital in Copenhagen by A. Gammergaard and co-workers (*Acta chir. scandinav.* [supp.] 245:307-314, 1959). The absence or presence of pulsation of the femoral arteries and angiocardiographic examination with injection of the contrast medium into the pulmonary artery were the most important diagnostic aids for the recognition of this type of coarctation. In the evaluation of the operability, the absence of pulsation of the femoral arteries was of great importance. Conventional roentgenographic and electrocardiographic examination did not aid in the diagnosis. Radical operation with resection of the coarctation was performed in 12 of the 20 infants, and 5 of these died. Patients who had ventricular hypertrophy, enlarged heart, a systolic pressure in the right ventricle exceeding 40 mm. Hg, and symptoms of insufficiency from birth had the poorest prognosis. Patent ductus arteriosus was present in 85% and ventricular septal defect in 50% of the patients. These complicating cardiac conditions aggravated the prognosis. Death occurred in 9 of the 10 patients with ventricular septal defect and in all patients with a right-to-left shunt referable to a patent ductus arteriosus or to a ventricular septal defect.

GERMANY

Chemoprophylaxis and Preventive Chemotherapy of Tuberculosis.—H. Spiess of Göttingen University (*Deutsche med. Wchnschr.* 84:1410-1415, 1959) differentiated between chemoprophylaxis and preventive chemotherapy. Chemoprophylaxis is the prevention of the development of an infection by a drug in a yet noninfected person, and preventive chemotherapy is treatment of an infected patient to prevent the development of the disease. Three objectives must therefore be considered in the prophylaxis of tuberculosis: (1) prevention of tuberculosis in the tuberculin-negative person, (2) prevention of the disease in the infected patient, and (3) control of possible early or late postprimary sequelae in the tuberculous patient. Isoniazid (INH) is now generally used for the chemoprophylaxis of the tuberculin-negative person. Only isolated results of INH prophylaxis in man are known so far. One report is of 14 infants who were given INH and para-aminosalicylic acid for prophylaxis because of familial contact with tuberculosis. Of these infants, 12 remained free of any signs of tuberculosis during a follow-up period of two years, one became tuberculin-positive, and one developed an exudative pleurisy.

Numerous animal experiments were undertaken in the line of preventive chemotherapy. All investigators agreed that the development of tuberculosis could be prevented by the use of INH. Long-term prophylactic treatment with 10 mg. of INH per kilogram of body weight daily is capable of suppressing a tuberculous infection or keeping it localized. Administration of this dose at least twice weekly prevents dissemination of the disease. The author believes that general prophylaxis in children and adolescents is not advisable because of organizational difficulties and because of the danger of shifting primary infection to a later age, but it may be desirable when contact with infective sources is known to have occurred and when it can be confined to a certain period. INH prophylaxis combined with BCG vaccination may be worth considering for exposed persons. The most effective method appears to be prompt BCG vaccination and revaccination six weeks after elimination of the source of infection if the tuberculin test result is negative. INH should be given for prophylaxis in the meantime.

Persons already infected should receive INH prophylaxis until the source of infection is removed, and BCG vaccination should be given four weeks later if the BCG test result is negative. Another possibility would be to use an INH-resistant strain of BCG and at the same time to give prophylactic doses of INH for eight weeks, when sufficient protection against superinfection should have developed. At any rate, all infected children under 3 years of age should be given 6 to 10 mg. per kilogram of INH daily for at least six months. Older children, with clinical or roentgenographic evidence of active tuberculosis, should be given INH in the same way for at least six months. For active processes, combination with other tuberculostatic drugs should also be considered.

The following recommendations were made: (1) chemoprophylaxis with INH for noninfected healthy subjects who are temporarily exposed to an increased risk of tuberculosis and for infants and small children in whom an infection is suspected; (2) preventive chemotherapy for persons of any age infected with tuberculosis when the infection was acquired in the previous six months, for all children below three years of age infected with tuberculosis regardless of the time of infection, and during puberty when signs of an exacerbation of a previous process are noted; and (3) for tuberculosis patients and during convalescence, preventive chemoprophylaxis of any active tuberculosis for at least six month and retreatment when there is danger of an exacerbation (measles, whooping cough, or influenza). Chemoprophylaxis is no substitute for BCG vaccination.

INDIA

Adrenal Steroids and Hepatic Failure.—C. C. Kapila and co-workers (*Indian J. M. Sc.* 14:76 [Feb.] 1960) stated that acute liver necrosis has so far been associated with a case fatality of almost 100%. Since the authors did not get good results with the use of glutamic acid preparations, they tried steroid therapy. Treatment consisted of full doses of tetracycline by mouth after a purgative or high enema. Tetracycline was used because it was the antibiotic least likely to cause vomiting. In order to meet the caloric requirements and to reduce endogenous protein breakdown to minimum, one liter of 5% glucose solution was given intravenously. From 0.5 to 1.0 liter of isotonic sodium chloride solution per day was given to compensate for urinary loss of electrolytes. A watch was kept for signs of potassium deficiency, and this was treated adequately if noted. Vitamin B complex and vitamin C were administered in large doses. Doses of 100 mg. of hydrocortisone were given every eight hours intravenously. As the condition improved this was given by mouth. Of the five patients so treated two were moribund on admission and died within 10 hours. The other three, however, survived.

A Dichloracetamide Compound for Amebiasis.—J. R. Shah and co-workers (*Indian J. M. Sc.* 14:92 [Feb.] 1960) stated that 18 to 43.5% of the population in Bombay has amebiasis. In a survey of 473 persons, amebiasis was diagnosed clinically in 136. On stool examination, 87 of these showed vegetative, cystic, or both forms of Entamoeba histolytica. These patients were given the dichloracetamide compound, Mebinol, in doses of 500 mg. three times a day for 10 days. Results were checked in 82 patients, after termination of therapy, by repeated stool examination. Clinical cure and protozoal clearance was seen in 91% at the end of three weeks. Follow-up for up to 12 weeks in some of the patients showed the cure rate to be 73%. Some of the apparent relapses may have been instances of reinfection. Although there were no significant side-effects of the drug, some patients complained of flatulence, loss of appetite, and abdominal discomfort.

Hydrochlorothiazide.—K. K. Datey and co-workers (*Indian J. M. Sc.* 14:135 [Feb.] 1960) gave hydrochlorothiazide to 12 patients (7 with congestive cardiac failure, 3 with hepatic cirrhosis, and 2 with nephrotic syndrome). Two of the patients with congestive cardiac failure had failed to respond to the usual treatment. After an observation period of 2 to 10 days with complete bed rest and a low salt diet containing known amounts of sodium and potassium, hydrochlorothiazide was given by mouth. With this treatment only two patients with cardiac edema required digitalis. Hydrochlorothiazide was given in an initial dose of 50 mg. once a day, increased to 100 mg., and then to 200 mg. a day, at intervals of two or three days, depending on the response. The total duration of therapy was 4 to 24 days. Four of five patients with congestive cardiac failure developed significant diuresis with loss of weight and clinical improvement. The two refractory patients who did not improve with mercurial diuretics also proved refractory to hydroclorothiazide. The two patients with nephrotic syndrome responded well.

Of the three patients with cirrhosis, one developed diuresis with increase in the urinary excretion of both sodium and potassium without any untoward effects, but the other two did not improve. The dose of 100 mg. a day was usually adequate in patients who responded to this drug. Electrolytic balance studies showed that although there was significant loss of potassium in the urine it was less than the loss noted when chlorothiazide therapy was used. The danger of hypokalemia must always be remembered. The drug seemed to precipitate hepatic coma in two of the three patients with liver disease. For the rest it was found to be as potent a diuretic as chlorothiazide, and one-tenth of the dose usually required of the latter drug was found to be sufficient. The danger of hypokalemia should be guarded against, as it is only slightly less than that when chlorothiazide is used.

Irradiation of Malignant Cells.—Sundaram and Rijhsinghani (*Indian J. M. Sc.* 14:201 [March] 1960) observed the behavior of malignant cells during the course of irradiation therapy in 10 patients with oral cancer. Total radiation dosage was 4,200 r. The authors divided malignant cells into three types according to the amount of nucleolar ribonucleic acid present. Type 1 consisted of daughter cells with minimal ribonucleic acid (RNA), type 2 of cells with late interphase nuclei (LIN) with well marked RNA, and type 3 of degenerating cells with an excessive accumulation of RNA.

The pretreatment smears from the lesions showed a similar pattern in the 10 patients with an abundance of cells of types 1 and 2 and only a few cells of type 3. In spite of this cytological similarity before treatment, the response to irradiation varied. In seven patients the number of type 1 cells decreased while an increase in type 2 cells persisted until the end of treatment. This response was considered inadequate; this was also borne out by follow-up studies of six patients, each of whom had a local recurrence within a few months. The remaining three showed a different cytological response. With the disappearance of type 1 cells, type 2 cells diminished in number early in the course of treatment, and the later smears contained only type 3 cells. This response was considered favorable, and clinically all of the patients were cured, with no evidence of recurrence during a follow-up period of one year. The type 1 cells represented a state immediately preceding cell division.

Suppression of mitotic activity after irradiation was indicated by a decrease in, or absence of, this type of cell. The course taken by type 2 cells in late interphase nuclei was uncertain. Some divided again to produce malignant cells, while others underwent degeneration. Persistence of this type of cell after irradiation was considered an adequate response with a possibility of local recurrence, while complete disappearance of these cells indicated a favorable prognosis. This method could, therefore, be useful in evaluating the chances of curability in malignant neoplasms.

Penicillin Inactivation.—Sarkar and Lahiri (*J. Indian M. A.* 34:306 [April 16] 1960) stated that the failure of penicillin to produce its therapeutic effect in certain patients may be due to the development of resistance by the causative organisms or to failure of the host's defense mechanism to supplement the activity of the drug. They investigated the possibility of yet another factor, the inactivation of penicillin by the serum of patients who had received penicillin previously. For this investigation, serums from 26 patients with a definite history of previous penicillin administration, a doubtful history, and with no history of previous injections were studied. Thirteen of 14 patients with a definite history of previous penicillin therapy and 2 of 6 patients with a doubtful history were observed to have the power to inactivate varying amounts of penicillin. Such power was not present in the serum of any of those with no history of previous injections. In patients whose serum contains penicillinase a compensatory adjustment of the dosage schedule may have to be made.

Filaria Control.—About 4,375,000 people have received treatment under the National Filaria Control Program. After therapy, reactions have varied in incidence and severity in the population treated. Over 22 million persons have been covered by sample surveys. A number of new filarial foci have been revealed by these surveys. It has also been found that filariasis is not confined to urban areas, as hitherto believed, but is endemic in many rural parts also. The findings thus indicate that the problem of filarial endemicity in India is far in excess of the original estimate that 25 million people are exposed to the risk. According to the revised estimate, the population at risk may exceed 40 million.

Giant Cysts of the Lung.—R. Mahadevan (*Indian J. Surg.* 22:13 [Feb.] 1960) said that although giant cysts of the lung are not common, they occur more frequently than is generally believed. He has observed 13 such cases in a series of 140 patients with bronchiectasis and cystic disease of the lung. The youngest was 3½ years of age and the oldest was 63. Nine of the 13 patients were admitted with a diagnosis of lung abscess and 2 suffered from recurrent attacks of spontaneous pneumothorax. Most of them had cough with foul expectoration and fever. Two were being treated mistakenly for pulmonary tuberculosis, and in one an incorrect diagnosis of empyema was made. In five the condition was associated with recurrent attacks of hemoptysis. Three patients with repeated bouts of chills and fever had been treated for malaria for a long time before they were admitted, and one of them who also had attacks of diarrhea was treated for amebiasis.

This condition is serious if left untreated. Except for one girl in this series who had mitral stenosis, all underwent operation. Eight did well and four died. These deaths were caused by cardiac arrest, hemorrhage, status asthmaticus, and severe tension pneumothorax in the contralateral (healthy) lung respectively. Dyspnea by itself, however severe, should not be considered a contraindication for operation as it is due to the thoracic cavity being too small for the size of the cyst and is relieved as soon as the chest is opened. Resection is dangerous in extremely dyspneic patients only if the roentgenogram shows the cyst to be on the more efficiently ventilated side of the chest. A one-stage resection of an infected cyst was also found to be hazardous, and these patients did well when the infected cavity was first treated by open thoracotomy and drainage; this was later followed by excision of the cyst or resection of the affected portion.

Tests for C-Reactive Protein and Antistreptolysin.—Barua and Mukherjee (*J. Indian M. A.* 34:301 [April 16] 1960) noted that there have been conflicting reports regarding the value of the test for C-reactive protein (CRP) in diagnosing and assessing rheumatic heart disease as compared to such procedures as determination of sedimentation rate and leukocyte count. Some workers have noticed the association between active rheumatic heart disease and a rise in the titer of antistreptolysin O in the serum. The authors have reported here the results of evaluation of the test for CRP in ischemic and rheumatic affections of the heart and such other diseases as tuberculosis, malignancy, parasitic diseases, infectious diseases, cirrhosis of liver, bronchial asthma, and endocrine disorders.

Tests for antistreptolysin O were made only in patients with rheumatic heart disease. Routine measurements of sedimentation rate and total and differential leukocyte counts were also made. The study included 22 healthy men, 12 women with normal pregnancies of different duration, and 153 patients with different diseases. The titer for antistreptolysin O was determined in the serums of 24 patients with rheumatic heart disease and 5 healthy adults. CRP could not be detected in the healthy men and normal pregnant women. The sedimentation rate was elevated during pregnancy even in the first trimester. The CRP value would thus be of help in detecting tissue destroying lesions associated with pregnancy when the sedimentation rate would be of no help.

Most of the patients with myocardial infarction in this study came to the hospital rather late, thus delaying the investigations. All of them showed neutrophilic leukocytosis in the first few days; the count returned to normal in 10 days. The sedimentation rate was raised in most patients and remained high even when CRP disappeared from the serum. All of the patients showed presence of CRP in the serum in the acute stage of the illness. CRP could be detected in some before the sedimentation rate showed a rise. It usually disappeared during the second or third week although it persisted longer in some patients. The authors believed that this test for CRP had no special advantage over the simpler procedures in myocardial infarction.

CRP could be detected in 8 of 10 patients with active rheumatic heart disease. In 9 of these the sedimentation rate was elevated and in 9 the leukocyte count was increased. The antistreptolysin O titer was raised in six of them. In 20 patients with clinically inactive rheumatic heart disease CRP was found in 4, the sedimentation rate was high in 11, leukocytosis was found in 4, and the antistreptolysin O titer was raised in 13. Thus none of the tests done singly could be relied on to indicate rheumatic activity. No correlation between the different tests was observed. CRP was, however, found to be a better index than the sedimentation rate, which remained high even in patients whose disease was inactive. CRP could almost always be found in patients with malignant tumors but was of little diagnostic or prognostic value because of its lack of specificity. It was not found constantly in persons with the other diseases studied except in those with such acute infective illnesses as typhoid. The presence or absence of CRP depended on the degree of tissue destruction, and the test could not be of any help in the diagnosis of these conditions.

Hypoferremia and Edema After Antimegaloblastic Therapy.—M. S. Narayanan (*J. Indian M. A.* 34:267, [April 1] 1960) studied the changes in serum iron levels made after treatment with single injections of vitamin B_{12} and folic acid. Thirty-eight patients from the poorest class who had macrocytic anemia with elevated mean cell volume, varying degrees of bone marrow changes, and histories of defective nutrition were used for this study. Of these, 14 were in relapse. The marrow examination showed variations from a predominantly normoblastic reaction to a typical megaloblastic hyperplasia. Four normal subjects without any hematological disorder and six patients with iron-deficiency anemia served as controls. The serum iron level was determined before and at repeated intervals after the injection.

Most of the patients with typical megaloblastic marrow showed an early and significant fall in serum iron level after the injection of vitamin B_{12}. This was followed by an adequate reticulocyte response. Administration of folic acid resulted in a further fall in iron level and another reticulocyte increase. Most of the patients with an intermediate megaloblastic type of marrow did not show such marked changes in the iron level or in the reticulocytes with the administration of vitamin B_{12}. Folic acid led to a prompt fall in serum iron level with subsequent adequate reticulocyte response in only three patients. Patients with a normoblastic picture showed no significant change in serum iron level.

Similarly, changes in both types of control were insignificant. After treatment, edema developed in four of the patients in the series within a week of the vitamin B_{12} injection and in seven patients after folic acid administration. In these 11 patients, the serum iron level remained low without showing a tendency to rise after the initial fall. Thus a fall in serum iron level, which occurred only in patients with megaloblastic changes, indicated successful therapy. The degree of fall indicated the degree of response. The appearance of edema could be explained by the state of iron deficiency produced in these patients, as edema is associated more frequently with iron-deficiency anemia than with macrocytic anemia. Iron is an important aid to treatment of patients with macrocytic anemia.

NORWAY

Fatal Case of Tetanus.—The verdict of a law court was solicited in a claim for damages for the widow of a farmer whose death from tetanus was attributed to the omission of an injection of antitetanic serum a few hours after his left little finger was crushed on Oct. 29. The surgeon attending him at a hospital outpatient clinic found roentgenographic evidence of fracture and dislocation inflicted by metal parts of a hay press which had torn the nail almost free and soiled the wound with machine oil. The functions and sensation of the finger were still retained, and it was put up in plaster after irrigation with saline solution, primary wound suture, and reduction of the fracture and dislocation. As the wound had not been contaminated by earth, an injection of antitetanic serum was not given. When the patient was examined again on Oct. 31 the plaster was readjusted and 900,000 units of penicillin were injected. He was seen again on Nov. 2 and was told to return after 10 days for the removal of the sutures, but when he returned on Nov. 9 and the plaster was removed, the terminal phalanx was seen to be black and gangrenous. He died of tetanus on Nov. 12.

A professor of bacteriology and the head of the Oslo hospital emergency medical service were called to give evidence as experts in the suit for damages. They agreed that this was a borderline case in which the defendant hospital could not be convicted of negligence. In regard to the experiences of the Oslo hospital emergency medical service, its head said that in 1958 it dealt with about 13,000 acute lesions, about 5,000 of which involved hands and fingers, but tetanus antitoxin was given to only about 1% of these patients. The case is reviewed in *Tidsskrift for den norske laegeforening,* March 15, 1960.

Lidocaine for Periarthritis.—Local injections of lidocaine were given to 60 patients with humeroscapular periarthritis by Fretheim and Blikra (*Tidsskr. norske laegefor.,* April 1, 1960). First puncture of the subacromial bursa was followed by irrigation with saline solution during which calcified deposits were sometimes, but not always, evacuated. Hydrocortisone acetate or lidocaine was then injected. Greater relief was obtained by the injection of lidocaine than by that of saline solution, and the treatment came to be standardized with the injection of 9 ml. of a 0.5% solution of the drug to which 1 ml. of solution containing 25 mg. of hydrocortisone acetate had been added. Irrigation was then dispensed with, but a point was made of starting active movement at once.

In only a few cases was it necessary to give more than three injections, the intervals between which were usually three to seven days. Complete restoration to normal was effected in 90% and in only three patients did persistence of symptoms require operation. An acute relapse in two patients led to a repetition of the injections, which were as successful as before. In view of the prompt relief effected by lidocaine, it is doubtful that the cortisone was necessary, but emphasis needs to be put on the institution of active movements at the earliest possible moment. As for the comparative merits of x-ray and lidocaine treatment, relief of pain came sooner with the latter. The former is, however, effective in many patients.

SWEDEN

Surgical Treatment of Pulmonary Tuberculosis.—T. Bruce and co-workers (*Acta chir. scandinav.* [supp.] 245:63-70, 1959) studied a series of 621 patients with pulmonary tuberculosis who had a thoracoplasty (134 patients) or a resection (487 patients). The early complications noted were ventilatory insufficiency and cardiological and neurological disturbances. Ventilatory insufficiency requiring a tracheotomy and treatment with a respirator occurred in 15 patients and appeared after both thoracoplasty and resection. This complication was observed in persons who after functional tests were considered good risks. The cause was chiefly retention of secretion and exhaustion. Cardiac and vascular complications were manifested in disturbances of rhythm and conduction, pericarditis, and pulmonary embolism. Disturbances of rhythm and conduction (fibrillation and frequent ectopic beats) were found chiefly in older patients with cardiosclerosis. Pericarditis was observed only after left-sided pleural pneumonectomy.

Neurological complications included paralysis of M. serratus anterior with typical wing scapula on the side operated on, caused by damage to nervus thoracalis longus or a lesion of the cervical plexus on the opposite side with atrophy of M. trapezius and M. supraspinatus, and weakness in the shoulder joints. This type of paralysis was probably caused by pressure on the plexus owing to the patient's position during the operation. In all such patients good results were obtained with special gymnastics. The authors concluded that one runs the risk of becoming pessimistic in view of the value of a method of treatment when occupying oneself with the complications. In regard to operations for pulmonary tuberculosis such pessimism is uncalled for, because complications are surprisingly few in relation to the magnitude of the operations and the improvement achieved.

UNITED KINGDOM

Getting Married.—A revised version of the British Medical Association's shilling booklet, "Getting Married," which was withdrawn last year after a storm about its articles on sex, is on sale again. Last year's edition was severely criticized by indignant doctors and was withdrawn by the BMA Council. The association was left with 50,000 copies on its hands, and these were destroyed. The 1960 issue is quite innocuous and unlikely to be banned. Dr. Winifred de Kok, who edited last year's edition and who resigned from the BMA when it was banned, has not contributed to the new edition. The 1960 issue was edited by Dr. Harvey Flack, editor of *Family Doctor,* the BMA's monthly magazine for the laity. Dr. Pilkington's contribution warns that a person marries not one, but a whole clan, and that in-laws can be pretty fearsome.

Royal Army Medical Corps.—According to an annotation in the *British Medical Journal* of April 9, after more than 20 years conscription will soon be a thing of the past. The Armed Forces are preparing to return to an all-regular composition. In the R. A. M. C. promotion up to the rank of major will be made according to length of service and promotion to lieutenant colonel and higher ranks will be made by selection. The regular cadre of the future R. A. M. C. will be larger than it was before World War II, and the proportion of posts in the rank of lieutenant colonel or higher will be about the same (42%) as it used to be, but the proportion of posts in the rank of colonel and above has been increased from 14 to 18%. This includes 18 posts in the rank of brigadier, which did not exist in the old establishment. Before World War II, there were six posts in the rank of major general (all nonspecialists), but in certain circumstances the number could be increased by up to four supernumerary appointments for specialists. From now on the number of major generals will be nine, five of whom will be nonspecialists, while the remainder will be the commandant of the Royal Army Medical College; three of the specialist directors will be at the War Office. One appointment of lieutenant general will continue to be filled by the Director-General of the Army Medical Services.

Teaching Social Medicine.—The *British Medical Journal* of April 16 contains an annotation on teaching social medicine which states that, following the example of London and Cambridge, the University of Oxford no longer includes public health as a subject for final examinations. The British Medical Students Association, however, published a report strongly favoring a full course in social medicine. Although in some of its aspects it could be integrated with some other subjects in the clinical curriculum, it should also be taught as a separate entity covering epidemiology, medical sociology, and the organization and working of the National Health Service. More emphasis should be placed on the social aspect of clinical cases in the wards. The report stressed the value of visits to factories, special clinics, and patients' homes, the latter being considered more instructive when made with a general practitioner or a visitor from the Health Service. The report further suggested that, although social medicine should not be included as a subject in the final examination, a combined examination in social medicine and infectious diseases would be suitable.

Standard Test for Drunkenness.—The use of a standard form of examination for drivers suspected of being under the influence of alcohol and a small portable machine to test reaction time were urged by Dr. A. S. R. Sinton, police surgeon for Leeds, at a symposium in London of the Forensic Science Society. He said that many physicians tended to use their own standards so that the degree of intoxication required for certification of drunkenness varied widely between doctors. Dr. Sinton believed that a police officer experienced in giving a standard examination could detect incapacity to drive as well as a police surgeon could. The standard examination of drunken drivers, introduced by the BMA, is satisfactory, but many doctors are not familiar with it. Police surgeons know that they may be put through a severe cross-examination in court. They resent having their opinion contradicted, whether by magistrate or by jury. In these circumstances they tend to testify only to certainties. Dr. Sinton suggested that such groups as the Association of Police Surgeons and the BMA should be asked to persuade members to certify drunkenness on minimum clinical signs based on a standard form of examination.

Inhibition of Food Absorption.—Weight reduction is usually achieved by reducing food intake or by the use of drugs that curb appetite. A new approach was made by J. A. Nissim (*Nature* 185:222, 1960), who accidentally discovered that a constituent of a well-known bactericide curbed food absorption in rats. He was examining the pharmacology of trimethylhexadecyl ammonium stearate, which is a constituent of the quaternary ammonium bactericide, cetrimide (B. P.). Rats receiving the substance showed a drastic loss in weight which was gained again when the drug was stopped and the animals had access to unlimited amounts of food.

The compound was given to a healthy man, who lost 20 lb. (9.1 kg.) while taking it. This loss in weight was reversible. According to Nissim, trimethylhexadecyl ammonium stearate causes loss in weight by interfering with food absorption. Histological changes were observed in the duodenum and jejunum of animals who were given the drug. Possibly it acts by interfering with enzyme action. If it only causes diminished absorption of food without interfering with the absorption of essential nutrients such as vitamins, electrolytes, and hematinic substances, it might have a place in the treatment of obesity.

Irritancy of Soap.—As a result of an investigation into the factor or quality which is responsible for the irritant properties of soap, Bettley and Donoghue (*Brit. J. Derm.* 72:167, 1960) concluded that the irritancy of soap depends in some degree on the presence of fatty acids of low molecular weight. They were unable to detect any irritant effect due to alkalinity. When both of these factors are eliminated, there remains an irritant property which is not simply the effect of detergency, as it is not equally found in a soapless detergent. Thus, they found that 1% Teepol, a soapless detergent consisting chiefly of alkyl sulfates, produced a negative reaction in 95% of 157 subjects; 73% had negative reactions with 1% toilet soap. When the Teepol was alkalinized to pH 10, however, the proportion of negative reactions decreased to 85%. This increased irritancy of alkalinized, as opposed to neutral, Teepol was attributed to the Teepol increasing the permeability of the outer layers of the epidermis, allowing the alkali to exert an irritant effect. The irritancy of soap, though partly caused by its fatty acid content, is also related to its ability to modify the epidermal barrier, which allows solutes to reach the malpighian layer more easily.

Imipramine and Iproniazid in Depressive States.—According to J. N. P. Moore (*Practitioner* 184:652, 1960) imipramine and iproniazid relieve a considerable proportion of endogenous depressions. A series of 115 patients with endogenous depression who were given imipramine were divided into three groups. Of 38 who had had chronic depression for more than one year and who had failed to achieve a sustained remission with electroplexy, 66% improved markedly with imipramine therapy. Of 22 who had had depression for less than one year and who failed to achieve a sustained remission with electroplexy, 90% improved markedly when taking imipramine. Of 55 with fresh depression, for the most part patients with milder cases not treated by electroplexy, 74% improved markedly with imipramine therapy.

The more closely the clinical condition corresponded to endogenous depression, the more certain it was that a remission would occur. In deeply depressed patients, especially those who were suicidal risks, it was usually unwise to use imipramine, or, if started, to persist with it if a swift response was not forthcoming. Such patients were still best treated with electroplexy, although there was some evidence that a combination of the two treatments might be more effective than either alone. The most troublesome sequel to imipramine therapy was a hypomanic state. Careful supervision of the administration of the drug to all deeply depressed patients is therefore indicated.

Iproniazid was given to 174 patients with endogenous depression. Of 70 who had failed to achieve a sustained remission with electroplexy, 48% improved markedly with iproniazid therapy. The corresponding figure for the 39 patients with depression of less than one year's duration who had failed to achieve a sustained remission with electroplexy was 60%, and for the 65 patients with fresh cases of depression, for the most part patients with milder cases not treated by electroplexy, 70% improved markedly. Side-effects with iproniazid therapy were more frequent and sometimes serious. Troublesome hypotension was common, and transient psychoses with excitement and paranoid trends occurred in six patients. The author concluded that although iproniazid was probably a less effective drug than imipramine where pure endogenous depression was concerned, it was more valuable when anxious, hysterical, or obsessional traits were prominent.

Weight Reduction.—Many diets for weight reduction for the obese are based on the statement by Kekwick and Pawan that, during short periods of isocaloric submaintenance diets, loss of weight is greater when most of the calories are supplied by fat instead of by carbohydrate. As they had not noted failure to absorb fat or changes in basal metabolic rate, they suggested that this difference was due to a specific dynamic action of fat that was much larger than had previously been observed.

These results were disputed by Pilkington and co-workers (*Lancet* 1:856, 1960). They repeated the experiments of Kekwick and Pawan, but for longer periods. Nine patients, all grossly obese, were given 800 to 1,000 calories a day. They were given three diets, high-carbohydrate, high-fat, and high-protein, each being adhered to for a period of 18 to 24 days. All patients lost weight on these diets, and no significant difference was found in the rate of weight loss, whatever the diet. The results were the same on a diet in which fat comprised 86% of the calories as on one in which carbohydrate comprised 91%. Over the period studied, isocaloric submaintenance diets, whatever their composition, were equally effective in producing loss in weight.

The authors attributed the results obtained by Kekwick and Pawan to dietary studies that were made over too short a period. The loss in weight could have been due to changes in fluid balance. On 800 and 1,000-calory diets, obese patients lose weight steadily over a period of about four months irrespective of the composition of the diet.

Venereal Disease in Teenagers.—At the annual congress of the Royal Society of Health, A. J. King and A. R. Wisdom reported that of 6,255 new cases of venereal disease at the Whitechapel Clinic (one of the largest such clinics in London) in the year ended June 30, 1959, 67% of the patients were in the infectious stage. Of these 490 were teenagers. They also reported that at Holloway Prison, the main prison for women in the London area, teenagers formed an increasing proportion of the prostitutes admitted. An as yet unpublished study by the British Cooperative Clinic Group, covering 147 venereal disease clinics, showed that there was a serious and increasing incidence of venereal infection in 1958 among young persons in the 18 to 19 year age group, which is greater than that for any other age group and well above the average increase for the country as a whole. Another speaker reported that the number of women attending one particular clinic in 1959 was almost double those attending 20 years before and that 20% of those attending were girls with office jobs; before World War II only 4% had been girls with office jobs. This same speaker reported that most girls admitted to initial sexual acts between the ages of 13 and 16.

CORRESPONDENCE

CYTOLOGICAL SCREENING TECHNIQUES

To the Editor:—Dr. Frank C. Coleman of the College of American Pathologists, in his presidential memo of April, 1960, states that an editorial on cytological screening techniques in THE JOURNAL, March 12, page 1165, "leaves the impression that mail order cytology is as effective as a cytologic program carried out by private physicians." He counsels members of the College of American Pathologists that "if this editorial or the P. H. S. report on which it is based is used to promote a mass screening program in cytology or mail order cytology in your area you will be in a position to set the record straight." The part of the "record" which Dr. Coleman quotes is a telegram to him from Dr. J. R. Heller which states that "At present, P. H. S. believes mail order cytology and large case-finding cytology clinics for cancer of cervix should be performed only under conditions of research need or where there is no possible alternative."

For a large number of physicians in most areas of the United States there is no alternative but to resort to the mail when they wish to offer patients the benefit of cytological screening. Some physicians may not be affiliated with a medical institution having a cytological diagnostic service. Others, wishing to select diagnostic services on the grounds of competence, reliability, and speed of reports, may prefer private cytology laboratories. It is a fact that speedy services prevail among independent laboratories, which is in the best interest of physician and patient. Evidence of the need for and the lifesaving potential of Papanicolaou's method is too well known to require elaboration. It is equally clear that local pathologists alone cannot provide this service in person for all of the women of the United States.

The mailing of smears to private laboratories is the only solution. The use of the term "mail order" in connection with a professional service is unfortunate because of the totally unfounded connotation of inferior quality. It is understood that a private cytology laboratory is staffed by professional cytologists working under the supervision of a qualified pathologist (and not all pathologists are automatically qualified as cytologists). A well-run independent cytology service uses methods and criteria identical with those of a well-run cytology division of a department of pathology, to which surely no one can object. The use of the mail instead of hospital messengers and the use of the telephone for consultation where necessary surely will not affect the reliability of the laboratory. Cytology incompentently done is to be condemned regardless of where it is done; but no one can object to competent, reliable, commercial diagnostic laboratories, and cytology competently done under these conditions deserves as much recognition as that done in hospitals.

The facts presented by the Public Health Service (publication no. 671, Jan. 1959) clearly contradict Coleman's opposition to mass screening programs in cytology or "mail order" cytology programs. The first paragraph of the quoted P. H. S. publication states: "Results from a 10-year 'mail order' cytologic screening program for uterine cancer have confirmed the value of the cytologic test and show that an effective case-finding program can be carried out by private physicians who mail specimens to a central screening laboratory." The paper concludes as follows. "Finally, they suggested that a mass cytologic screening for uterine cancer is equally effective whether carried out entirely by private physicians on a mail order basis, or by large, public, metropolitan clinics." Rather than to oppose cytology screening programs and the use of the mail to increase their effectiveness, such organizations as the College of American Pathologists would be well advised to intensify their "vital leadership and support of community cancer programs," which Dr. Heller recognized, by taking the initiative in developing standards for private cytology services and aiding in the development of new methods designed to enhance reliability and effectiveness of widely applied cytology.

THE JOURNAL is to be congratulated on having called to the attention of physicians the documented practicability of wider cytology screening. The specialists most concerned with diagnosis, the pathologists, should follow this lead and promote the widest possible application of this method, which cannot be kept from American women by a negative opinion such as that implied in the presidential memo.

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IMPACTION IN THE ESOPHAGUS

To the Editor:—In the article "Impaction of Food Bolus in the Esophagus" in THE JOURNAL, April 23, page 1922, reference is made to the use of digestant agents for the treatment of food boli impacted in the esophagus. I would like to point out that the use of such agents in patients with impaction in the esophagus must be approached with caution. Andersen and co-workers (*Ann. Otol. Rhin. & Laryng.* 68:890 (Sept.) 1959) reported an instance of fatal perforation of the esophagus which occurred in a 27-year-old woman after the use of a digestive solution (Caroid) for meat impaction in the esophagus.

After experimental investigations prompted by this incident, Andersen postulated that stretching and compression of the esophageal wall, resulting from impaction, caused sufficient ischemia for the proteolytic enzyme (papain) in the digestant to act. In this connection it is of interest to refer to studies by Derrick and his associates (*Surgery* 43:486 (March) 1958) in which it was determined that the bursting strength of the intact human esophagus is about 3.0 to 7.5 lb. per square inch. This critical pressure tends to be reduced to 1.0 to 2.25 lb. per square inch in conditions leading to ulceration and removal of esophageal mucosa, as would compression resulting from impaction.

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QUININE WATER AND MYASTHENIA GRAVIS

To the Editor:—In the past several years there has been a steady increase in the use of beverages containing quinine, known variously as tonic or quinine water. Part of this increase in consumption results from advertising and part from the fact that during warm weather this type of beverage has certain advantages over the sweet carbonated type. Since patients with moderate to severe forms of myasthenia gravis are very sensitive to the curare properties of quinine salts, I wonder if it would be a particular hazard for these patients to drink this beverage in warm weather. I recently heard that in Sweden an 11-year-old girl with severe myasthenia gravis had a temporary exacerbation of her symptoms after the ingestion of a bottle of quinine water.

With this report in mind the staff of the A. M. A. Council on Foods and Nutrition was consulted. The five leading distributors of tonic water that were contacted in the United States, including one overseas company, were very cooperative. I was much impressed with the interest and courtesy shown by the manufacturers of these beverages. The care and precautions taken to ensure constancy in the chemical contents, including many spot analyses with efficient and modern electronic equipment, was most reassuring. Quinine salts, either as the hydrochloride or sulfate, were reported in milligrams per ounce (32 cc.), in parts per million, or percentage by weight. The amounts were all between 2.1 and 3.8 mg. per ounce. This averages to 3 mg. per ounce, 100 parts per million, or 0.01%. Therefore, in a 10-oz. bottle of tonic there is only 30 mg. of the quinine salt. The equivalent of a 5-grain tablet (300 mg.) could not be ingested unless one drank 10 bottles of the beverage in a short period of time. It is unlikely that any normal person would have any side-effects, symptoms, or harm from the ordinary ingestion of one or even two bottles of the beverage in a short time, but patients with myasthenia gravis might be sensitive to 1/10 or even 1/20 of the amount that would affect normal persons. Thus, one or two bottles of such a beverage might produce an exacerbation of their myasthenic symptoms. I would therefore suggest that patients with this disease be instructed by their physicians to avoid this beverage in amounts of over one bottle and preferably limit their intake to 5 to 6 oz. at a time. In this way it is almost inconceivable that they will have any difficulty.

I have not encountered in my practice any evidence of harm from the normal ingestion of quinine water. The caloric content of the sugar in this beverage varies from 9 to 12 calories per ounce, so that a 10-oz. bottle would have between 90 and 120 calories. Diabetics or other patients on a strict low-calorie diet should take note of the caloric value of this beverage.

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THE STEMMA OF HARVEY

A delayed reply by Mr. Bennett Cerf of Random House, Inc., regarding the stemma of Harvey in "Great Men of Medicine" by Ruth Fox (*J. A. M. A.* 172:1393 [March 26] 1960) reveals that the "baffling" reference was due to a transposition of a line. The reference should have read as follows. "In 1602 Harvey left Italy and returned to England. He had made himself a name at the University. It was customary to install tablets called *stemmata* around the walls of the building to commemorate important professors and students. Harvey's *stemma*, a white-clad arm holding a candle entwined by a snake, is a little worn with the passage of three hundred and fifty-odd years, but it is still to be seen in Padua."—ED.

MEDICAL FILM REVIEWS

Lumbar Disc Excision and Vertebral Body Fusion by the Anterior Route: 16 mm., color, sound, showing time 17 minutes. Prepared in 1958 by and procurable on loan from Paul H. Harmon, M.D., Kaiser Foundation Hospital, 2425 Geary Blvd., San Francisco 15.

The method used by the author for removal of the intervertebral disk and lumbosacral fusion, approached along the abdominal route and performed extraperitoneally, is presented by this film. A saline solution of 9 cc. is used to determine the degree of degeneration of the disk. If that quantity of liquid can be introduced in an intervertebral disk, no doubt the degree of degeneration can be ascertained on x-ray films, particularly those made when the patient is in a vertical position. However, the spurs on the anterior adjacent margins of the vertebrae, which are demonstrated by the x-ray films, indicate the degeneration of the disk. Hence, the determination of the volume of saline solution seems to be unnecessary. Apparently this operation is performed from the opposite portion of the intervertebral disk for intraneural protrusion of nucleus pulposus. There is no visualization of the neural canal, and it is questionable whether the nucleus pulposus is symptomatically responsible. Bone bank bone, which is dead bone used in the fusion of the vertebral bodies, may not be vascularized and may slough into the pelvis. The bone graft's sloughing, in close proximity to the vascular structures in that particular area, may cause complications which are associated with irritation or injury of these structures, unless fusion is performed by experienced surgeons and precautionary measures are taken. The claim is made that twice the amount of intervertebral disk may be removed by this method, but removal may also be performed by the more conventional posterior methods. It is unnecessary to remove the annulus fibrosus and the attached portions of the intervertebral disk. In regard to alleviating the symptoms, it is the separated protruded portion of the nucleus pulposus of the intervertebral disk which is the offender. The film states that there is bony union, but the oblique film of one case showed a large radiolucent area between the fifth lumbar vertebra and the sacrum, and no trabeculations were present in this area. Possible pseudoarthrosis was not ascertained. The summarized description of the film stated that there were 400 operations of this kind performed. The narration and photography of the film are good. This abdominal approach is unique and undoubtedly could be performed in the hands of an experienced surgeon, but it cannot be recommended for use by orthopedic or neurosurgeons because there are simpler techniques with a posterior approach which offer satisfactory results.

Resuscitation of the Newborn: 16mm., color, sound, showing time 25 minutes. Prepared by the Special Committee on Infant Mortality of the Medical Society of the County of New York. Produced in 1960 by Sturgis Grant Productions, New York. Procurable on loan from Smith, Kline & French Laboratories, Medical Film Center, 1500 Spring Garden St., Philadelphia 1.

"Resuscitation of the Newborn" is based on a report by the Infant Mortality Committee of the New York County Medical Society and illustrates the essential principles and techniques for resuscitation of infants who do not breathe or whose respiration is irregular at birth. The film describes the physiology of prenatal and postnatal oxygenation and states the factors that may contribute to producing respiratory depression in the newborn. The film then depicts—through live action in the delivery room and animation—the procedures and apparatus necessary for effective resuscitation. By diagram the placental and neonatal circulation are clearly portrayed. The processes by which respiration is initiated and also depressed are well illustrated. The essentials of the examination during pregnancy are briefly touched upon. More emphasis is directed to good obstetrical care during labor with special observation as to what is happening to the infant to be born. The usual procedures for aspiration of nasopharyngeal fluids and stimulation of respirations in the normal neonate are given. The Apgar scoring system is demonstrated by which the circulatory, respiratory, and neurological status of the newborn infant can be evaluated. There is a good demonstration of the stimulation of respiration by sole-heel slapping as well as by laryngoscopic examination and aspiration. Intratracheal tube passage and aspiration, stimulation of respiration by mouth breathing into the intratracheal tube and positive pressure apparatus such as a pressure bag or a mechanical positive pressure machine are also shown. It is emphasized that the positive pressure exerted by whatever means must be low. These procedures and the indications for them are clearly shown. The color photography in this motion picture is of a very high quality; all scenes are sharp and clear, and the color rendition is excellent. Effective animation is used throughout the film to make each procedure thoroughly understood by the viewer. This is an authoritative film, highly recommended for medical students, all house officers, obstetricians, pediatricians, general practitioners, and all those having anything to do with the delivery and care of newborn infants.

ABSTRACTS FROM THE LITERATURE

INTERNAL MEDICINE

Peptic Ulcer and Hyperparathyroidism: A Survey of 300 Ulcer Patients. B. Frame and W. S. Haubrich. A. M. A. Arch. Int. Med. 105:536-541 (April) 1960 [Chicago].

Three hundred patients admitted to the Henry Ford Hospital on a diagnosis of peptic ulcer were screened for hyperparathyroidism. In each patient the serum calcium and inorganic phosphorus concentrations were determined. These tests were repeated if they exceeded the normal range (calcium greater than 11 mg. per 100 cc. or phosphorus less than 3 mg. per 100 cc.). An estimate of the renal tubular reabsorption of phosphorus (TRP) was made for 125 consecutive patients in the total group. The TRP test was also applied to all others who exhibited abnormal serum calcium or phosphorus values. All antacids were withdrawn 24 to 72 hours before the test. It has been shown that the ingestion of aluminum gels reduces the absorbable phosphorus and decreases the urinary phosphorus excretion, thereby influencing the rate of renal tubular reabsorption.

Four patients were found to exhibit hyperparathyroidism. A parathyroid adenoma was resected in each of these 4 patients. During the 18-month period encompassing this study, only 4 additional diagnoses of hyperparathyroidism were recorded. Therefore, half of the patients with hyperparathyroidism had peptic ulcer. The difficulties in the evaluation of calcium and phosphorus metabolism in active peptic ulcer patients on high calcium and phosphorus diets and antacids can be surmounted. The most practicable method of screening such patients for hyperparathyroidism would be a simple serum calcium and phosphorus determination. If suggestive leads are obtained, then the more involved tests of parathyroid function may be utilized. Single determinations should not suffice. Rather, repeated observations of the biochemical data over a period of time must be obtained before the diagnosis of hyperparathyroidism is completely excluded. The authors recommend that patients with peptic ulcer be screened for hyperparathyroidism.

Lowering of Serum Lipid Concentrations: Mechanisms Used by Unsaturated Fats, Nicotinic Acid, and Neomycin: Excretion of Sterols and Bile Acids. G. A. Goldsmith, J. G. Hamilton, and O. N. Miller. A. M. A. Arch. Int. Med. 105:512-517 (April) 1960 [Chicago].

Adults with hypercholesterolemia were maintained on isocaloric diets of ordinary foods which furnished 115 Gm. fat, of which 90 Gm. was supplied by butter and cream (saturated fat) or by corn oil (unsaturated fat). After a control period of 3 or more weeks on the diet containing saturated fat, some subjects received nicotinic acid in doses of 1 to 2 Gm. 3 times daily for 3 or more weeks; other subjects received neomycin, 0.5 mg. 4 times daily, for a similar period. After the medication was stopped, the diet furnishing saturated fat was continued for at least 3 additional weeks. Then the diet was changed to one which furnished unsaturated fat (90 Gm. corn oil) and the entire regimen was repeated. Serum-lipid levels, cholesterol content, phospholipid levels, and total esters were determined twice weekly.

Concentrations of cholesterol, phospholipid, and total esters in serum decreased when the diet was high in unsaturated fat and after administration of neomycin or nicotinic acid. Lowest levels were observed with a combination of unsaturated fat and either medication. Substitution of unsaturated for saturated fats in the diet resulted in a 20 to 25% increase in excretion of bile acids and a moderate increase in excretion of sterols with a change in the ratio of cholestane to coprostane compounds. Administration of neomycin was followed by a 3-fold to 4-fold increase in bile-acid excretion during both dietary regimens. Nicotinic acid had no effect on fecal excretion of bile acids or sterols.

Hepatocellular Jaundice as a Complication of Iproniazid Therapy. L. E. Rosenblum, R. J. Korn, and H. J. Zimmerman. A. M. A. Arch. Int. Med. 105:583-593 (April) 1960 [Chicago].

This report is an analysis of the records of 90 patients in whom jaundice developed while they were being treated with the amine oxidase inhibitor, iproniazid. The drug had been given for 4 weeks or longer in 77 of the patients, and the longest period of administration was about 6 months. The average daily dose ranged from 25 to 150 mg. The

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total dose varied, but most patients received between 1 and 10 Gm.

Twenty of the 90 patients died, and all but 1 of the 20 deaths could be attributed to the hepatic disease, but the deaths could not be correlated with the dosage of iproniazid or the duration of therapy. The results of studies described in this report and by earlier investigators indicate that the jaundice associated with iproniazid administration is hepatocellular in type. It is characterized by abnormal thymol turbidity and cephalin flocculation test results and by mild increase in serum alkaline phosphatase levels. The degree of elevation of serum transaminase values is characteristic of that seen in hepatic necrosis. Onset of the hepatic dysfunction appears to be insidious, with anorexia and dark urine as the usual initial complaints. Tests reflecting early jaundice and hepatocellular damage, such as urine bilirubin, serum bilirubin, and glutamic oxalacetic transaminase levels, might be useful in detecting early iproniazid toxicity.

Digitalis Antagonism: **Part II. A. C. Keyl, J. R. Suker, H. U. Wessel, and P. S. Rhoads. A. M. A. Arch. Int. Med. 105:709-726 (May) 1960 [Chicago].**

Studies on dogs indicated that monopotassium glutamate was more effective and safer than other salts in reversing the toxic response to digitalis. A clinical study was conducted on patients with different types of arrhythmia and subjected to digitalis therapy. Electrocardiograms were taken before and after the clinical evaluation, and preinfusion blood samples were obtained. A solution of 900 cc. of 5% dextrose-water to which 100 cc. of 25% monopotassium glutamate were added (final concentration of 0.135 mEq. of potassium per cubic centimeter) was infused into a brachial vein at a rate of 2 to 4 cc. per minute. Electrocardiographic monitoring of lead 2 was instituted during the infusion, and a complete electrocardiogram was taken on completion. Abnormal changes due to digitalis intoxication and apparent in electrocardiograms were corrected at relatively low levels of from 10 to 20 mEq. of potassium. The drug seemed to be relatively safe in presence of altered renal function, with no unfavorable reaction during or after the infusion. Electrocardiographic signs of hyperkalemia disappeared rapidly when the treatment was discontinued.

An Effective Treatment of Refractory Ascites in Cirrhosis of the Liver. **A. G. Redeker, O. T. Kuzma, and T. B. Reynolds. A. M. A. Arch. Int. Med. 105:594-600 (April) 1960 [Chicago].**

Eighteen patients with cirrhosis of the liver and a history of prolonged, excessive alcoholic intake were the subjects of this study. All patients had severe or moderately severe ascites which had been present either constantly or recurrently for periods of from 2 months to 2 years. The basis for selection of patients for this study was failure of sodium diuresis during the administration of chlorothiazide in doses of 2 Gm. per day. Some patients had, in addition, received organomercurials and ammonium chloride without manifesting a diuresis. All of the patients were hospitalized for the entire period of the study. Dietary sodium was restricted as rigidly as possible to approximately 300 mg. per day.

The combined administration of chlorothiazide and 6-methyl prednisolone (6-MP) induced a marked sodium diuresis in 15 of the 18 patients. Neither chlorothiazide nor 6-MP exerted a natriuretic effect when administered alone. Urinary sodium excretion averaged 3 mEq. per 24 hours during chlorothiazide administration alone and increased to an average of 56 mEq. per 24 hours when both compounds were administered concurrently. No complications were observed in this study from the prolonged administration of either chlorothiazide or 6-MP.

Perforation of the Right Ventricle During Selective Angiocardiography. Report of a Case. J. L. Doppman, R. Shapiro, G. L. Wilson, and others. J. Thoracic & Cardiovas. Surg. 39:500-504 (April) 1960 [St. Louis].

The authors report on a 26-month-old girl in whom perforation of the right ventricle occurred during selective angiography. The authors consider the position of the catheter to be the most important factor conducive to perforation. The advantages of the National Institutes of Health (N. I. H.) catheter, which was used in this instance, as compared with the older type Cournand catheters, justify the associated risk in using it. The following recommendations are made to help prevent this complication. Blind manipulation of the catheter should be avoided. The time during which the catheter remains in unchanged position within the heart should be reduced to a minimum. Advancing the catheter deep into the apex of the right ventricle places the tip against the junction of septum and ventricular wall. The slight apical elevation accompanying each systole may impale the thin right ventricular apex on the rigid, relatively sharp-tipped N. I. H. catheter.

In studying right ventricular outflow tract problems, the catheter tip should be advanced well into the outflow tract, so that its course describes the characteristic U-shaped configuration. If a satisfactory U-shaped bend cannot be achieved, the catheter should be partially withdrawn under fluoroscopic control to a point just distal to the tricuspid value. If a more proximal injection is desired, for example, to show an interventricular septal defect, the catheter tip should be positioned slightly distal to the atrioventricular valve as determined by pressure readings. Under no circumstances should the catheter be advanced until resistance is met and then allowed to remain deep in the right ventricular apex.

The Endocrine Eye Lesion in Hyperthyroidism: Its Incidence and Course in 165 Patients Treated for Thyrotoxicosis with Iodine^{131}. H. E. Hamilton, R. O. Schultz, and E. L. de Gowin. A. M. A. Arch. Int. Med. **105**:675-685 (May) 1960 [Chicago].

The incidence of eye lesions in hyperthyroidism was studied on 165 patients (27 men and 138 women, their ages ranging from 14 to 80 years). Goiters were diffuse in 58.2% of the patients, nodular in 16.3%, and indeterminate in 25.5%. Myopathy occurred in 23% and pretibial myxedema in 3%. The amount of radioactive iodine (I^{131}) necessary to control the hyperthyroidism was 1 dose in 51.5% of the patients, 2 in 30.3%, and 3 or more in 18.2%. The average single dose was 4.6 mc. The response to the therapy was prompt, and the euthyroid state was attained within 4 months or less. Endocrine eye lesions (lid retraction, visible tissue reaction, and disturbance of ocular motility with attending symptoms) were present at some time in 73% of the 165 patients. The symptoms were lacrimation, pain, pressure, burning, diplopia, and decreased visual acuity. There was prompt improvement of the eye symptoms in 106 patients after treatment with I^{131}. Temporary aggravation was observed in 14 patients who did not complete the therapy and in 7 who had already attained the euthyroid state. A comparison of the changes in protrusion with other eye signs indicated that in 91.8% of the patients the endocrine signs improved or disappeared, while ocular protrusion remained the same or progressed.

Evaluation of Some Clotting Tests in Patients Receiving Coumarin Drugs. W. J. Messinger and M. Weiner. A. M. A. Arch. Int. Med. **105**:727-732 (May) 1960 [Chicago].

A study of the 1-stage prothrombin test was made at a coagulation laboratory. Blood specimens were collected in uncoated glass tubes, and 1 part of 3.8% sodium citrate was added to 9 parts of blood. Prothrombin time was determined for whole plasma and for plasma diluted in a 12.5% saline solution. Recalcification time and heparin tolerance were determined, and the antithrombin activity was estimated. Blood specimens obtained from 3 normal subjects and 5 patients receiving hypoprothrombinemic agents were divided into 40 tubes and code-labeled. Estimation of the prothrombin time in the 40 specimens showed excellent reproducibility. Plasma specimens from 122 patients on anticoagulant therapy were subjected to the same tests. Recalcification time and heparin tolerance were altered by coumarin drugs, although little correlation was found between heparin tolerance and prothrombin estimations. Bleeding occurred in 6 patients during the anticoagulant therapy; in only 1 instance did the heparin tolerance test reflect an excessive clotting response not indicated in the simple prothrombin test. Determination of prothrombin activity of diluted plasma provided an early clue for anticipation of bleeding in some patients. The 1-stage test is highly reproducible and remains the most adequate test for clinical evaluation of the effect of coumarin-type anticoagulants. A periodic monitoring of all clinical laboratories engaged in prothrombin determination should be the rule.

The Sicca Syndrome (Sjögren's Syndrome): A Study of Sixteen Cases. C. W. Denko and D. M. Bergenstal. A. M. A. Arch. Int. Med. **105**:849 (June) 1960 [Chicago].

The authors report on 14 women and 2 men, between the ages of 32 and 62 years, with the sicca syndrome, or Sjögren's syndrome, who were seen in the Arthritis Clinic of the University of Chicago. The main clinical features included hypofunction of the lacrimal and parotid glands with a chronic polyarthritis and, in addition, general symptoms such as fatigue. Eight of the patients had findings of definite, probable, or possible rheumatoid arthritis, while in the other 8 patients no diagnosis of rheumatoid arthritis could be made. Dryness of the mouth or eyes occurred in all patients. The most striking laboratory finding was the dysproteinemia manifested by the presence of abnormal levels of serum gamma globulin, C-reactive protein, and cryoglobulin. Biopsy specimens illustrated the typical parotid infiltration with lymphocytes and increased connective-tissue formation. The most satisfactory treatment consisted of the combined administration of prednisone and desiccated thyroid. The etiology of this disorder remains unknown but a sensitivity mechanism or hyper-reactivity is suggested because of the marked dysproteinemia and multisystemic involvement.

Prevention of Recurrent Rheumatic Fever in Children and Adults with Oral and Repository Penicillin. T. W. Mou, H. A. Feldman, and H. Hartenstein. Am. J. M. Sc. **239**:403-416 (April) 1960 [Philadelphia].

This report is based upon the first 3 years of experience of a rheumatic fever prophylaxis clinic which was organized in 1955. The patients were admitted to the clinic only if they had rheumatic heart disease or diagnosis of previous acute rheumatic fever. At the first visit, a detailed history was obtained, the patient was examined and assigned to either the oral or repository group by alternation. Prophylactic treatment by the oral method consisted of daily doses of 200,000 units of benzathine penicillin G; by the repository method it consisted of intramuscular injections of 900,000 units at monthly intervals.

A total of 139 patients with either rheumatic heart disease or a history of previous rheumatic fever, were subjected to these prophylactic regimens. Each regimen appeared to be effective in preventing clinical Group A streptococcic infections and recurrent acute rheumatic fever. Modest increases in antistreptolysin-O (AS-O) titer were noted with equal frequency in the 2 treatment groups and were unrelated to clinical illness. These increases were most apparent in the spring months.

There was a constant downward progression of the median AS-O values for the entire population during the observation period, except that some minor increases were observed during the fall-winter season. Allergic reactions were of little consequence except for 1 episode of anaphylaxis after an initial injection. Postinjection pain and discomfort were common but were not a deterrent to repeated injections.

Gastrodialysis in the Treatment of Acute Renal Failure. T. A. Marr, J. M. Burnell, B. H. Scribner, and W. R. Koreski. J. Clin. Invest. 39:653-661 (April) 1960 [New Haven, Conn.].

In the past, gastric lavage has failed as a method of dialysis because of uncontrollable electrolyte transfers and loss of large amounts of fluid. The use of a cellophane bag has made gastrodialysis technically possible. A method of continuous dialysis, as compared with intermittent dialysis, might obviate the fluctuations in the uremic state inherent in intermittent dialysis. Further, if continuous dialysis were sufficiently effective it might be possible to avoid the costly, time-consuming, highly technical procedure of hemodialysis, or it might decrease the number of hemodialyses necessary to sustain the patient through a period of renal failure.

Gastrodialysis is carried out through a cellophane bag which is tied to the end of a nasogastric tube and swallowed. Dialysis fluid is placed in the bag and changed every 20 minutes thereafter. The dialysis is usually continued 24 hours a day until renal function improves. The dialysis fluid should be warmed to body temperature. In 14 patients (12 adults and 2 children) with acute renal failure, gastrodialysis was performed for varying lengths of time ranging from 2 to 16 days, with a mean of 6 days. Data were obtained in 98 balance periods ranging from 20 minutes to 24 hours, but averaging 12 hours.

The method proved safe, practical, and without serious complications. Although probably the least efficient of present-day methods of dialysis, gastrodialysis has proved useful in acute renal failure. Gastrodialysis is satisfactory as a means of regulation of osmolarity, extracellular volume, and acid-base status. Dextrose can be given by the alimentary route, without administration of water. The removal of nitrogen and potassium does not compare favorably with extracorporeal dialysis. However, in patients without a large catabolic load, gastrodialysis appears adequate to prevent hyperkalemia and to avoid or decrease the number of hemodialyses required. Gastrodialysis, to be effective, must be begun early and continued throughout the acute renal failure. Hemodialysis should be available in case gastrodialysis proves inadequate.

Hiatal Hernia: Diagnosis and Medical Management. L. W. Leiter. J. Maine M. A. 51:105-107 (April) 1960 [Portland, Me.].

The pain of hiatal hernia may mimic that of angina, including shoulder and arm radiation. With such a distribution, a physician can be further influenced to diagnose coronary artery disease if, as often occurs, the pain is worse with activity (especially bending and lifting) and after meals. Recumbency may provide an important clue, for hiatal hernia pain is apt to occur or to be aggravated by assuming the recumbent position. Pyrosis in association with pain would suggest esophageal origin, as would dysphagia. Pain may be predominantly midepigastric, may radiate through to the back and left subscapular area, is often burning, pressure-like, aching, or described as a fullness. Secondary symptoms result from complications—bleeding, ulceration, perforation, or obstruction.

Uncomplicated symptomatic hiatal hernia requires regulation of the mechanical factors, and an ulcer regimen, in an effort to reduce the acid-pepsin factor when reflux does occur. Much can be accomplished by explaining to the patient the anatomic features and the nature of the mechanical factors. These patients should not take large meals, but rather 6 small meals daily; they should not wear constrictive abdominal supports; bending or lifting should be avoided, especially after meals; the head of the bed should be elevated on 6-inch blocks; recumbency after meals should be avoided; obesity and constipation should be corrected.

Surgery is seldom necessary in hiatal hernia; in general, the indications are similar to those for operation in peptic ulcer disease, that is, hemorrhage, perforation, intractability, and obstruction. With acute hemorrhage from hiatal hernia, surgery is usually indicated, although in a patient who has never been on a medical regimen, if the bleeding is minimal, a period of conservative treatment and observation is worthwhile. Chronic anemia from hiatal hernia, where both blood loss and interference with elaboration of intrinsic factor may be mechanisms, should have the benefit of surgical repair. Dramatic results can be anticipated.

Reduction of Serum Cholesterol by Sodium Dextro-Thyroxine. P. Starr, P. Roen, J. L. Freibrun, and L. A. Schleissner. A. M. A. Arch. Int. Med. **105**:830 (June) 1960 [Chicago].

The authors report on 43 outpatients in attendance at the Los Angeles County Hospital, the Good Hope Clinic, and the private offices of two of the authors. Eleven of these patients had corrected, partial, or complete hypothyroidism; 13 were euthyroid patients who had diabetes mellitus. Seventeen patients had idiopathic hypercholesteremia, and 2 patients had familial xanthomatosis. Sodium dextrothyroxine was administered to these patients orally in daily doses varying from 2 to 16 mg. for periods of 6 months to more than 1 year. The serum cholesterol level was reduced, and kept down, in all the patients but 1. In patients with original cholesterol values above 400 mg. per 100 cc. the average result was 251 mg. per 100 cc. In those with original values between 300 and 400 mg. per 100 cc. the average result was 242 mg. per 100 cc. In those whose original values were between 200 and 300 mg. per 100 cc., the average result was 194 mg. per 100 cc. The sodium dextro-thyroxine treatment seemed to reduce the serum cholesterol level about as effectively in patients with diabetes mellitus and idiopathic hypercholesteremia as in those with hypothyroidism. These effects were associated with a gradual rise of basal metabolic rate in patients with athyreosis, but were not associated with medicamentous thyrotoxicosis in euthyroid persons. In fact, there was little symptomatic indication of the striking biochemical change.

Diet and the Abdominal Crisis in Essential Hyperlipemia. R. I. Nachman. Rhode Island M. J. **43**:247-249 (April) 1960 [Providence].

Essential or idiopathic hyperlipemia is a relatively rare disease of fat metabolism characterized chemically by a marked increase in the total serum lipids, most predominantly in the neutral fat fraction. Approximately 90 cases have been reported in the literature. One of the outstanding clinical features of the disease, seen in over half the reported cases, is recurrent abdominal pain sometimes closely simulating an acute surgical abdomen. The 25-year-old man, whose history is presented, gave a history of recurrent attacks of abdominal pain, since the age of 15. The attacks occurred at intervals of 10 to 15 weeks and were characterized by severe stabbing, colicky pains in the right lower and right upper quadrants of the abdomen, lasting at times up to 24 hours. He was hospitalized on different occasions, during which time repeated gastrointestinal x-ray studies were negative. In 1957, grossly milky serum was noted. The diagnosis of chronic relapsing pancreatitis was made. However, there was no elevation of serum lipase or amylase.

The patient's military service was punctuated by intermittent attacks of acute abdominal pain. On repeated examinations he was found to have milky serum. The pattern of serum lipid changes could be correlated with the amount and type of fat in the diet. An abdominal crisis was precipitated on a high fat diet following a steady progressive rise in the serum cholesterol. A high fat diet consisting of 60% unsaturated fatty acids failed to produce an abdominal crisis. A trial of steroid treatment with a low fat diet produced a downward trend in the serum lipids with a pronounced fall in the phospholipids. A sustained low fat diet is the treatment of choice in essential hyperlipemia.

Renal Involvement in Progressive Systemic Sclerosis (Scleroderma). R. J. Levine and B. R. Boshell. Ann. Int. Med. **52**:517-529 (March) 1960 [Lancaster, Pa.].

The authors report on 3 men and 2 women, 28 to 59 years of age, with renal involvement in progressive systemic sclerosis (scleroderma) who were admitted to the Peter Bent Brigham or the Robert Breck Brigham Hospital in Boston. The duration of progressive systemic sclerosis before clinical renal involvement varied from 1 to 2 years in 4 patients, and it was 23 years before the onset of the acute renal lesion in the 5th patient. The duration of life after the clinical onset of acute renal lesions varied from 16 to 30 days. Autopsy was performed on 4 patients. A characteristic triad of lesions was observed in the kidney: (1) intimal proliferation of the small intralobular arteries and arterioles; (2) fibrinoid necrosis involving the walls of the afferent arterioles and sometimes the glomerular loops; (3) focal cortical infarctions. Although the renal involvement may run a benign protracted course, as it did in the 5th patient, with evidence of long-standing renal damage such as glomerular hyalinization and interstitial fibrosis, the more common and significant manifestation of the lesion is an acute renal failure with relentlessly progressive oliguria and azotemia, often associated with a malignant form of hypertension, which was observed in 3 of the 4 other patients. In 1 patient the renal lesion developed without an elevated blood pressure. The course, when this acute renal lesion becomes clinically manifest, is unremittently downhill. Currently available methods of therapy are not apparently effective. It has been suggested that administration of adrenal steroid or corticotropin (ACTH) may even be harmful. It is unlikely however, that the prevalent use of corticosteroids for patients with progressive systemic sclerosis is responsible for all the renal lesions, since typical lesions occurred in 3 of the 5 patients, none of whom had taken these hormones within the 6 months previous to onset of renal failure.

Clinical Results of Treatment of Diabetes Insipidus with Drugs of the Chlorothiazide Series. J. D. Crawford, G. C. Kennedy, and L. E. Hill. New England J. Med. 262:737-743 (April 14) 1960 [Boston].

Diabetes insipidus usually is due to lack of the neurohypophyseal hormone, vasopressin, which enables the kidneys to form concentrated urine. Treatment consists of administering vasopressin from animal sources intranasally, sublingually, or intramuscularly. Some patients with hormone insufficiency become intolerant of or refractory to animal extracts. These patients, and those with the nephrogenic form of the disease in which the kidney fails to respond to the endogenous hormone, have stimulated the search for other forms of treatment. Chlorothiazide and some of its analogues have been shown to reduce the polyuria of diabetes insipidus.

The authors report their experiences with the drugs of the chlorothiazide series. Their 7 patients with diabetes insipidus included 1 with the congenital nephrogenic type. All responded with a prompt reduction in the amount of fluid taken voluntarily and in the quantity of urine passed, and body hydration has remained normal. Urinary osmolarity has been about doubled so that for the group as a whole, the renal water requirement has fallen by 47%. The drugs augment the influence of vasopressin and permit a considerable though subnormal dilution of urine in response to overhydration. Continued treatment appears not to cause sustained sodium deficit, hypotension or reduction in glomerular filtration rate, though potassium deficiency occurs unless an appropriate dietary supplement is ingested.

There appears to be little indication for the use of these drugs in patients normally responsive to vasopressin, but in nephrogenic diabetes insipidus or hormone insufficiency, in which the patient is intolerant of or refractory to vasopressin, further cautious exploration of their usefulness is in order.

Glaucoma Detection: A Problem for General Medicine. J. A. Buesseler. Missouri Med. 57:447-449 (April) 1960 [St. Louis].

Blindness from glaucoma can usually be prevented or arrested by early diagnosis and treatment. "Open-angle" or so-called chronic simple glaucoma poses the major problem. There is no pain or visual disability in the early stages of this disease; however, the increase in ocular tension of a mild to moderate degree is a measurable early sign. In the past, the ophthalmologist has borne the major burden for glaucoma detection. Unfortunately, victims of glaucoma frequently have not referred themselves to an eye physician until after far-advanced and irreversible damage has been done to the visual apparatus.

To prevent these tragedies of late diagnosis in glaucoma, the general practitioner occupies a key position in any realistic detection program. The determination of ocular tension by means of a tonometer must be incorporated into every physician's routine physical examination on patients over 30 years of age. Once glaucoma has been detected, the ophthalmologist must meticulously evaluate the individual case in regard to the type of glaucomatous process involved, the degree of impairment of the hydrodynamic mechanism in the eye, and the manifestations of damage to the visual system of the patient.

SURGERY

A Polyurethane Polymer (Ostamer): Its Use in Fractured and Diseased Bones. M. P. Mandarino and J. E. Salvatore. A. M. A. Arch. Surg. 80:623-627 (April) 1960 [Chicago].

The authors report on 35 patients who have been treated with a polyurethane foam (Ostamer) for fractured and diseased bones. In 28 of these patients healing was uneventful. In 5 the lesion continued to drain, but bony proliferation was proved by roentgenologic examination. Two patients in whom the tibia was involved were therapeutic failures.

Results showed that Ostamer has the strength and the adhesiveness necessary for bone fixation, and it also provides a chemical lacunar system. New bone not only climbs along the surface but grows through the plastic, as would be expected with an autogenous graft. This permits earlier ambulation and a more rapid return to a physiologic norm than other forms of treatment. The use of Ostamer in bone cysts, preamputation cases, and terminal malignancies with pathological fractures is suggested.

Carcinoma of the Esophagus with Metastases to the Base of an Active Peptic Ulcer. A. M. Markowitz and S. G. Weissman. A. M. A. Arch. Surg. 80:438-441 (March) 1960 [Chicago].

The spread of esophageal carcinoma to the stomach has generally been regarded as due to lymphatic permeation, via the submucous and the subserous lymphatics, or both. Many cases must be regarded as having spread in this way rather than as transplantations on the gastric mucosa from autoimplantation of detached fragments. The authors present an unusual instance of carcinoma of the esophagus with metastases in the area of a chronic bleeding and obstructing pyloric ulcer. This patient, an 80-year-old man, had a high degree of gastric acidity. Gastrointestinal examinations revealed a constricting lesion of the middle third of the esophagus which was interpreted as carcinoma. There was a large ulcer crater in the duodenal bulb. Esophagoscopy revealed a friable mucosal mass. Biopsy was reported as showing squamous cell carcinoma. The patient began to vomit "coffee-grounds." Exploration of the abdomen revealed many large, hard nodes near the cardia of the stomach as well as in the preaortic area which were interpreted as metastatic carcinoma. There was a hard mass surrounding the deformed duodenum. A palliative subtotal gastrectomy was performed. Examination of the surgical specimen revealed a large chronic ulcer in the pyloric channel at the gastroduodenal junction. At the base of the ulcer there was infiltration by squamous cell carcinoma. There was a benign gastric ulcer, but there was no evidence of metastatic spread. Radiotherapy was used postoperatively on the esophageal carcinoma. Roentgenoscopy indicated regression of the esophageal carcinoma and a well-functioning gastroenterostomy. The patient felt well and had no further episodes of gastrointestinal hemorrhage.

Pathological findings suggested that this invasion of the duodenal ulcer probably originated in the serosal surface of an adjoining involved lymph node. Whether the surrounding tumor precipitated the recurrent ulcer or whether the recurrent ulcer was the result of the high acidity cannot be decided. Although intraluminal transplantation of carcinoma cells in the colon appears to be well substantiated, this does not seem to be the case in upper gastrointestinal neoplasms. In the esophagogastric area the spread of esophageal carcinoma to the stomach appears to be via the lymphatic route.

Cancer Cells in the Blood Stream. L. Long, S. Roberts, R. McGrath, and others. A. M. A. Arch. Surg. 80:639-645 (April) 1960 [Chicago].

This study, which is a continuation of a paper reported in J. A. M. A. (155:1549 [Aug. 28] 1954), has been amplified to include the examination of whole blood samples collected during the observation and treatment of 328 patients with malignant disease and 35 patients with various benign diseases, in order to elucidate certain prognostic and therapeutic features. Arbitrary division of patients into 105 "curable" and 223 "incurable" patients showed that 24 of the former and 73 of the latter had malignant cells in the peripheral blood. The percentage of positive cases was somewhat higher in blood samples obtained from veins draining the tumor. Patients with incurable or nonresectable malignancy of the gastrointestinal tract had cancer cells in the peripheral blood, but there were no cancer cells in the blood stream of patients with curable disease. This indicates the probable role of the liver in destruction of cancer cells carried to this organ in the portal flow. When this capacity for destruction is overcome, the patient is no longer "curable." It is emphasized that absence of malignant cells does not necessarily mean that the lesion is operable, since local spread of the tumor and imperfect methods for finding these cancer cells must be considered.

Serial blood samples were drawn at frequent intervals before, during, and after various operative procedures in order to evaluate the response to surgery. Showers of cancer cells were isolated during such operative procedures as dilatation and curettage of the uterus, hysterectomy, laparotomy, radical mastectomy, nephrectomy, and various excisional procedures. It is therefore suggested that any manipulation, whether diagnostic or operative, which might cause showers of cells to enter the portal or general circulation be avoided.

Massive Gastrointestinal Hemorrhage Due to Prolapse of Pyloric Gastric Mucosa in a Child: Report of a Case. C. H. Fredell. A. M. A. Arch. Surg. 80: 1052 (June) 1960 [Chicago].

The 5-year-old boy whose history is presented had passed a black stool containing blood and had vomited 2 pints of blood shortly before admission. Intensive antacid and antispasmodic therapy was started, and blood transfusions were given. Barium studies of the upper gastrointestinal tract revealed pyloric obstruction. Laparotomy disclosed that a soft mass filled the first portion of the duodenum. Pylorotomy was done in the belief that a polyp was present, but the mass proved to be a complete circumferential prolapse of edematous ulcerated pyloric gastric mucosa. There was brisk bleeding from multiple small ulcerations. A hemigastrectomy and gastroduodenostomy was done. This extensive treatment was well tolerated. Massive gastrointestinal bleeding in children requires the same treatment as it does in adults.

Preoperative "Dumping Studies" in Peptic Ulcer Patients. D. B. Hinshaw, E. J. Joergenson, and C. E. Stafford. A. M. A. Arch. Surg. 80:738-742 (May) 1960 [Chicago].

Preoperative "dumping studies" were made on 50 patients with peptic ulcer by the rapid injection of hypertonic glucose solution into the upper jejunum through an intestinal tube. Observations were made with regard to the magnitude of the clinical reaction, the plasma volume fall, the peripheral blood flow and skin temperature changes. The same studies were performed on 30 of these patients after the operation but the provocative meal was given by the oral route instead of the intestinal tube. The majority of the patients had negative or mild reactions which showed that they were able to tolerate the rapid intrajejunal ingestion of hypertonic material without significant symptoms.

In the 10 women of this series a larger percentage of moderate to severe reactions was observed than in the group as a whole. This suggests that women are especially susceptible to dumping symptoms. The comparison between the clinical reactions in the 30 patients in whom both preoperative and postoperative studies were completed showed in each instance the same results before and after the operation, so that it is possible to predict by means of the "dumping tests" whether a patient with peptic ulcer is likely to have a severe dumping syndrome after gastrectomy. The tests should prove helpful in the selection of patients for surgery and should also help to determine what operative procedure may be best suited to a given patient.

Clinical Experiences in the Treatment of Tetanus. W. A. Altemeier, W. R. Culbertson, and L. L. Gonzalez. A. M. A. Arch. Surg. 80:977 (June) 1960 [Chicago].

Of the 123 patients with tetanus observed by the authors during the last 18 years, none had received a series of toxoid immunization injections, because, although the effectiveness of toxoid immunization has been definitely established, only a relatively small percentage of the civilian population has been immunized against tetanus. While, in the experience of the authors, passive immunization with 1,500 units of tetanus antitoxin has been effective, none of the 123 unimmunized patients had received such a prophylactic injection of antitoxin, partly because 13.8% had no history of a wound or injury and 35.8% had such minor injuries that their seriousness had been discounted by the patients or their physicians. The development of clinical tetanus in 7 of the 123 patients after delayed surgical procedures or remanipulations on compound fractures, long after the initial injury, is emphasized. The prolonged viability of Cl. tetani was demonstrated also by the fact that Cl. tetani could be cultured from tissues excised from an old wound 1 year after the injury. The patient who recovers from tetanus cannot be presumed to have developed immunity to the disease. The authors recommend that such patients should be given a series of toxoid injections to establish active immunity.

The chief cause of death in patients with tetanus has been acute respiratory arrest during a convulsion. Since 1946 the authors have focused the treatment of patients with tetanus on the prevention and control of respiratory arrest by around-the-clock emergency care and the use of thiopental sodium solution for elevating the threshold of excitability and securing quicker and more effective relief of convulsions and seizures of respiratory arrest. With this plan of management the mortality has been reduced from 65.1% to 21.2%. The use of thiopental is recommended.

Surgical Aspects of Thyroiditis. W. F. Pollock and D. H. Sprong Jr. A. M. A. Arch. Surg. 80:720-732 (May) 1960 [Chicago].

The authors report 97 patients with goiter due entirely or predominantly to thyroiditis. There were 90 women and 7 men, ranging in age from 11 to 76 years. The average age of the women was 41 years, and that of the men 47 years. Several patients had had medical treatment before operation without benefit, and all patients had been subjected to thyroid operations at intervals ranging from 2 to 26 years prior to that for Hashimoto's thyroiditis. It is apparent from the literature and from the patients of this series that there are many pitfalls in the accurate diagnosis of thyroiditis. The disease occurs more frequently in women than does any other thyroid disorder. Surgical management of Hashimoto's thyroiditis has definite advantages over medical treatment in that the risk of developing a malignancy in the intensely stimulated remnants of thyroid epithelium is prevented by their removal. The pressure symptoms are relieved, and the uncertainty regarding the precise diagnosis can be resolved on firm histological grounds. The removal of the source of the antigen breaks the antigen-antibody cycle and terminates the process of autoimmunization. All patients who have been operated on for Hashimoto's thyroiditis should be given thyroid medication orally after the operation.

Results of 1,000 Consecutive Basal Ganglia Operations for Parkinsonism. I. S. Cooper. Ann. Int. Med. 52:483-499 (March) 1960 [Lancaster, Pa.].

The author reports on 1,000 patients with paralysis agitans (Parkinson's disease, or parkinsonism) who underwent surgical intervention on the basal ganglions in St. Barnabas Hospital, New York. The operations, which were performed either by the author or by residents under his immediate supervision, consisted of occlusion of the anterior choroidal artery, chemopallidectomy, or chemothalamectomy. Of the patients subjected to chemopallidectomy or chemothalamectomy, 80% obtained relief of tremor, rigidity, deformity, and attendant symptoms such as bradykinesia and abnormalities of gait and posture. Twenty-four of the 1,000 patients died, representing a mortality of 2.4%. The incidence of hemiparesis or hemiplegia was less than 3%. The tremor, rigidity, and deformity of paralysis agitans can be completely relieved by this type of surgery. Five years later many of these patients were still symptom-free.

Clinical physiological testing of a reversible lesion placed in the thalamus or other site within the basal ganglions is essential if one hopes to produce consistent relief of parkinsonian tremor and rigidity and to maintain a low incidence of risk. This clinical physiological testing must be combined with correct roentgenoanatomic localization of lesion placement, and the lesion in each case must fit the requirements of the particular patient. The site of the lesion of choice for relief of tremor and rigidity is the region of the ventrolateral nucleus of the thalamus. Such a lesion includes the reticular nucleus of the thalamus, the zona incerta, and afferent fibers to the thalamus from the globus pallidus, cerebellum, red nucleus, and vestibular nucleus, as well as the efferent fibers to the cerebral cortex.

Patients in the 7th and 8th decades of life may be operated on with the same possibility of benefit as may those in the younger groups, provided that they do not have any intellectual or psychological abnormalities and that they have relatively few symptoms except for tremor or rigidity, or both, and the disabilities which these symptoms produce. Surgical treatment of parkinsonian tremor and rigidity is now indicated relatively early in the course of the disease.

Adrenalin and Noradrenalin-Producing Tumors of the Adrenal Medulla and Sympathetic Nerves. McC. Goodall and C. Stone. Ann. Surg. **151**:391-398 (March) 1960 [Philadelphia].

The fluorometric method of Euler and Floding was used to measure epinephrine (adrenalin) and arterenol (noradrenalin) levels in 24-hour urine specimens, which were collected from 505 patients. Idiopathic hypertension was present in 90 to 95% of the patients, and pheochromocytoma was suspected in the remainder. Pheochromocytoma was diagnosed in 11 patients (2.2%). All patients with tumor were operated on and, after excision of the tumor, showed the usual dramatic cure. Approximately ⅔ of the tumors were arterenol-producing tumors and ⅓ epinephrine-arterenol-producing tumors. There were no purely epinephrine-producing tumors. The authors believe that urinary catecholamine determination is a superior diagnostic procedure to the various provocative and blocking tests currently in use.

Idiopathic Perforation of the Stomach in the Newborn: Report of a Case. G. D. Vermilya, F. A. McCue, and D. A. Cunningham. Virginia M. Month. **87**:202-204 (April) 1960 [Richmond].

The authors report on a 1-day-old boy who was sent as an outpatient to the Clinch Valley Clinic Hospital in Richmond, Virginia, because he had vomited blood in small amounts on 3 different occasions. He had been delivered spontaneously on the way to another hospital on the preceding day, and had been allowed to return home after 12 hours. Body temperature was 98.6 F (37 C). There was no further vomiting after the administration of 2 doses of 5 mg. of carbazochrome (Adrenosem) salicylate with vitamin K, although a small amount of blood was passed in a meconium stool. There was no diarrhea. Two days later the infant suddenly became worse and appeared to be in shock. The abdomen became markedly distended and tense. There was profuse vomiting. It was thought that the distention was due to acute dilatation of the stomach. A catheter was passed and a small amount of bloodstained milk curds was obtained. Twelve hours later the abdomen was still markedly distended, the pulse was almost imperceptible and the rate was 160 per minute. Rectal examination did not reveal any abnormality. A roentgenogram showed pneumoperitoneum indicating a perforated hollow viscus. The infant died despite aspiration of the peritoneal cavity, blood transfusion, and administration of oxygen.

Autopsy showed free air and fluid in the peritoneal cavity and generalized peritonitis. The entire greater curvature of the stomach was necrotic and perforated throughout. Grossly there was no obvious cause for this condition. Microscopic examination revealed that the serosa was overlaid by necrotic material and leukocytes. Sections of the stomach showed acute necrosis. The muscle was present in the region of the perforation and the pancreas did not show any abnormal change. Four criteria are necessary to make the diagnosis. The patient must be a newborn infant, not over a few days old. There must be no evidence of peptic ulcer and no evidence of trauma. There must be no evidence that perforation occurred as the result of intestinal obstruction, of a vascular lesion of the stomach, or of significant cerebral lesions. The only treatment of idiopathic perforation of the stomach in the newborn infant is early operation and suture of the perforation.

Primary Intraluminal Tumor of the Aorta Producing Malignant Hypertension: Successful Surgical Removal. A. A. Kattus Jr., W. P. Longmire, J. A. Cannon, R. Webb, and C. Johnston. New England J. Med. **262**:694-700 (April 7) 1960 [Boston].

A 22-year-old woman, examined for a gynecologic disorder, was found to have a blood pressure elevated to 150 mm. Hg. Six months later she was hospitalized with a blood pressure of 210/115 mm. Hg, bitemporal throbbing headache, and puffy eyelids. Retrograde aortography of the abdominal aorta suggested that the hypertension was due to a Goldblatt kidney. The left kidney was excised and found to be hypoplastic; no true renal artery was identified. The blood pressure dropped temporarily after the operation, but it soon rose to 200/115 mm. Hg. A diagnosis of aortic coarctation was made and the patient underwent further laboratory, fluoroscopic, and electrocardiographic tests. Thoracotomy was performed under hypothermia to 86.4 F (approximately 30 C). The aorta was clamped and a longitudinal incision was made, showing white tumor tissue. The tumor tail formed a complete cast of the lumen of the aorta down to its bifurcation, with projections entering the orifices of the renal arteries. The patient was responding soon after the closure of the skin incision; the temperature and the blood pressure gradually became normal.

The final pathological diagnosis was fibromyxoma arising from the intimal aspect of the distal arch of the aorta, with metaplastic cartilage and bone formation. The renal ischemia and clinical features of malignant renal hypertension had resulted from the projections of the long tail of the intraluminal tumor into the orifices of the renal arteries.

Sarcoma of the Stomach. I. R. Trimble and G. A. Harkins. Surg. Gynec. & Obst. 110:437-442 (April) 1960 [Chicago].

The author reports on 20 consecutive patients, 13 men and 7 women, between the ages of 19 and 70 years, with primary sarcoma of the stomach who were treated at The Johns Hopkins Hospital, Baltimore, between 1944 and 1953. Of these, 11 had lymphosarcoma (8 small round cell type and 3 reticulum cell type), 8 had leiomyosarcoma, and 1 had a neurofibrosarcoma. Ten of the 20 patients complained of peptic indigestion suggestive of ulcer. The disease was still in an early stage in some of these patients, and was advanced in others. Four patients with advanced disease had diffuse abdominal pain. Three patients showed weakness or loss of weight, or both. Two patients, seen in an early stage of their disease, were asymptomatic and the diagnosis of their tumors was made on routine gastrointestinal x-ray examination. A massive hemorrhage occurred in only 1 patient with a large but circumscribed tumor. Except for the 2 asymptomatic patients, the duration of symptoms varied from less than 6 weeks to 3 years. The significant signs and symptoms consisted of abdominal pain, weight loss, anorexia, vomiting, anemia, melena, occult blood in the feces, a definite or suspected abdominal mass, dysphagia, and hematemesis. Barium studies of the gastrointestinal tract were made in 18 patients, and a mass, often stated to be intramural, was observed in all. Three of the tumors were located predominantly in the cardia. The remaining 17 tumors were in the body of the stomach and were about equally distributed on the posterior surface, lesser curvature, and greater curvature; only 2 were on the anterior wall. Ten patients did not have demonstrable metastases. Seven had local extension either to lymph nodes or contiguous organs. Three had distant metastases.

All patients were operated on. Four patients underwent total gastrectomy, 8 subtotal gastrectomy, 3 wedge resection of the stomach, 1 sleeve resection of the stomach, and biopsy only was performed in 4. One patient died 9 days after the operation from complications of total gastrectomy, an operative mortality of 5%. Of 18 patients included in a 5-year follow-up study, 9 were alive and without evidence of recurrence 5 years or more postoperatively, a 5-year survival rate of 50%. The prognosis for sarcoma of the stomach is considerably better than that for carcinoma of the stomach.

The Double Portacaval Shunt in the Treatment of Cirrhotic Ascites. W. V. McDermott Jr. Surg. Gynec. & Obst. 110:457-469 (April) 1960 [Chicago].

The authors treated surgically 12 patients, between the ages of 39 and 82 years, with cirrhotic ascites, who were admitted to the Massachusetts General Hospital, Boston. Based on the concept that a postsinusoidal intrahepatic block is a major factor in the complex metabolic and hemodynamic derangements associated with the formation of cirrhotic ascites, the operative procedure consisted of a double portacaval shunt, devised with the objective of achieving maximal decompression of both the splanchnic and intrahepatic vascular beds. After adequate exposure and stripping of the portal vein and inferior vena cava, the double shunt was constructed by dividing the portal vein about 4 cm. from its bifurcation in the porta hepatis and anastomosing each end separately to the inferior vena cava. In 2 patients the anastomoses were constructed by the more standardized side-to-side method.

There were 2 postoperative deaths. In 9 of the 10 survivors, ascites were dissipated rapidly without the need for salt restriction or diuretic agents. One patient was classified as a failure because of occlusion of the shunt; the failure has to be considered a technical error, and a splenorenal shunt is planned for this patient. It seems clear that shunt surgery of a type which will afford satisfactory decompression of both the hepatic and splanchnic vascular beds can reverse the clinical picture of the thin, wasted, chronically ill, ascitic patient and will restore the abnormal metabolic and endocrinological pattern to normal.

Recurrent Laryngeal Nerve Injury During Thyroidectomy. P. Hawe and K. R. Lothian. Surg. Gynec. & Obst. 110:488-494 (April) 1960 [Chicago].

The authors report on 1,011 consecutive patients who were admitted to the David Lewis Northern Hospital, Liverpool, England, between 1949 and 1958, and on whom thyroid operations were performed. Routine preliminary exposure of the recurrent laryngeal nerve was adopted for these operations, bilateral exposure of this nerve being performed in 802 patients and unilateral exposure in 209. Paralysis of the vocal cords occurred in 28 patients. In 3 of these, it proved to be permanent. Despite the complicated anatomic course of the nerve and its branches, preliminary exposure of these structures is a practical surgical procedure. Direct laryngoscopy should be performed routinely at the completion of the operation. Gross lesions involving anatomic division of the nerve produce permanent paralysis, but such an accident can almost always be avoided by exposure technique. Minor degrees of injury, such as may be expected with any peripheral nerve of corresponding size in a carefully conducted operation, are usually well tolerated. If paralysis follows, it will probably prove temporary. Paralysis due to ligature or suture usually ends in recovery, provided that the material is removed. Very rarely paralysis first develops in the early postoperative period. Until more cases have been studied a guarded prognosis should be given, although probably recovery will follow. Late postoperative paralysis resulting from scar contraction appears to be very rare.

Dissemination of Cancer of the Colon and Rectum: Special Reference to 4 Cases of Local Implantation in Perineal Wounds. G. O. McDonald and A. R. Williamson. Dis. Colon & Rectum 3:117-124 (March-April) 1960 [Philadelphia].

Dissemination of cancer of the colon and of the rectum occurs through local invasion, through extension into the lymphatic vessels, through the veins draining that portion of the intestine involved by the tumor, and through implantation, or seeding, of cancer cells. Of 103 patients who underwent combined abdominoperineal resection for carcinoma of the rectum between 1948 and 1958, recurrence was observed in the perineum of 7 patients. In only 2 of the 7 patients were the recurrences due to implantation of cancer cells. Both of these patients had multiple recurrences. The 1st patient permitted removal of the initial recurrent lesion but refused surgical removal of the 2nd. The other patient had all 3 recurrent perineal lesions removed. The 1st recurrence was not discovered until more than 1 year after the abdominoperineal resection; this lesion was removed and a 2nd recurrence appeared 6 months later. Five months after the 2nd recurrence, or 2 years after the initial operation, a 3rd recurrence appeared. The patient is clinically free of malignant disease now, 3½ years after the initial operation.

The reported data suggest that more vigorous treatment of perineal recurrences may result in more survivals after surgical intervention for carcinoma of the rectum. The adjuvant use of systemically administered anticancer drugs (such as nitrogen mustard), local irrigation of the perineal wounds with anticancer chemical agents (such as a buffered 0.5% sodium hypochlorite solution), and ligation of the intestine above and below the lesion should be given a trial as methods to control cancer dissemination, in addition to the usual surgical procedures.

Treatment of Rectal and Colonic Polyps Showing Early Malignant Changes. N. W. Swinton and J. C. Snow. Dis. Colon & Rectum 3:113-116 (March-April) 1960 [Philadelphia].

Between 1945 and 1954, 1394 patients with benign mucosal polyps of the rectum and colon and 1709 patients with adenocarcinoma of the colon and rectum were treated at the Lahey Clinic in Boston. In an additional 135 patients with polyps of the rectum and colon the pathologist reported the finding of both polypoid and carcinomatous tissue. Of these, 42 (31%) were treated by local excision or fulguration of the lesions; in the remaining 93 patients (69%) the lesions were resected. The size of the 42 malignant polyps treated conservatively varied from 0.5 to 5.5 cm. in diameter, and they were located in the rectum and rectosigmoid in 24, in the sigmoid in 14, in the descending colon in 3, and in the transverse colon in 1. No recurrences were observed to date in the group of patients treated conservatively, and there were no operative deaths.

The data suggest that many benign mucosal polyps of the rectum showing early malignant changes histologically can be treated safely by conservative methods. Polyps showing definite invasion of the stalk or adjacent bowel wall should be treated radically. The authors are not in complete agreement with Spratt, Ackerman, and Moyer who reported recently that there is no evidence to support the view that there is an intimate relationship between benign mucosal polyps and cancer. Until there is further evidence to the contrary, the authors believe that benign mucosal polyps of the colon and rectum have a malignant potential and should be removed or destroyed when discovered. There is, however, need for further clinical, and especially pathological, study of this problem.

NEUROLOGY & PSYCHIATRY

Observations on Deep Cerebral "Localization" of the Tremor of Parkinson's Disease. S. Mullan. A. M. A. Arch. Neurol. 2:274-280 (March) 1960 [Chicago].

The authors operated on 14 patients with paralysis agitans (Parkinson's disease), in 4 of whom tissue necrosis was produced in the brain by alcohol, and in 10 by a beta-emitting isotope, palladium-109. In 8 patients the treatment was bilateral. The position of the deep cerebral target relative to the posterior clinoid process was calculated in 3 dimensions by pneumoencephalography, and a needle was introduced which has a side-opening near the tip. From this opening a polyethylene catheter is protruded. By calculated rotation of the needle and calculated extrusion of the catheter, any point within a centimeter of the axis of the needle can be accurately reached. The tip of the catheter conveys the alcohol or carries the isotope. Sixty-six needle punctures were performed in the 14 patients. With 42 needle punctures there was little or no alteration of symptoms. With 24 needle punctures tremor was immediately abolished. Although the unsuccessful punctures were widely scattered throughout the globus pallidus, internal capsule, and part of the thalamus, the sites of the 24 successful ones were concentrated in an area 2 to 3 cm. behind the anterior commissure, 1.5 to 2.5 cm. lateral to the midline, and 0 to 1 cm. above the anterior commissure-pineal line.

Of the 14 patients, 1 is slightly worse because of mental dulling, and 1 has died. In 1 patient no lesion was made. The remaining 11 patients all show signs of improvement of tremor, or of rigidity, or both. Isotope implantations, the effects of which are quite predictable, are preferred to alcohol injections. It is easier to obtain good relief of tremor than good relief of rigidity by lesions at this thalamus-capsule site of election. Lesions produced in the globus pallidus have, in this small group of patients, been disappointing in their results.

Embryonal Atresia of the Fourth Ventricle: The Cause of "Arachnoid Cyst" of the Cerebellopontine Angle. W. J. Gardner, L. J. McCormack, and D. F. Dohn. J. Neurosurg. 17:226-237 (March) 1960 [Chicago].

The authors report on 3 men aged from 26 to 33 years and 1 16-year-old boy with embryonal atresia of the 4th ventricle. In the 3 men, the resulting malformation of the hindbrain consisted of a small cerebellar hernia and bilateral diverticula communicating with the 4th ventricle by way of the foramen of Luschka. In the boy, the malformation consisted of a small cerebellar hernia and a loculated cyst, the wall of which was lined by ependymal cells; the cyst occluded one foramen of Luschka. The authors' observations in these 4 patients, combined with those reported by Gardner and co-workers in 3 patients aged from 24 to 34 years, in 1957, show that atresia of the 4th ventricle in embryonic life may result in the following deformities of the hindbrain in the adult: Arnold-Chiari malformation; diverticulum of the foramen of Magendie (Dandy-Walker malformation); diverticulum of the foramen of Luschka; cyst of the foramen of Magendie; cyst of the foramen of Luschka; cerebellar hernia together with a membrane occluding the foramen of Magendie; varying combinations and degrees of the above malformations. These deformities of the hindbrain in the adult patient may be accompanied by basilar impression, congenital scoliosis, and syringomyelia.

Parasagittal Meningiomas of the Longitudinal Sinus and Falx. J. C. White, R. S. Schwab, and I. Sahinalp. J. Neurosurg. 17:197-212 (March) 1960 [Chicago].

The authors report on 25 patients with parasagittal meningiomas of the longitudinal sinus and falx who were operated on during the last 20 years. There was 1 operative death, caused by excessive loss of blood; 1 patient was lost to follow-up, and 3 have been operated on within the last 20 months. The remaining 20 patients were followed for from 3 to 20 years after the initial surgical intervention. Beside the one surgical death, death from sepsis occurred in another patient 3 months after the 4th operation for recurrence, after failure of the irradiated scalp to heal. These 2 deaths represent a low mortality of 8% of all patients and 4.3% of those operated on. Residual postoperative cerebral damage in the 23 survivors consisted of hemiplegia in 2, hemiparesis in 2, sensory deficit in 1, dysphasia in 2, and homonymous hemianopsia in 3, which relatively low morbidity is the result of modern operative and anesthetic techniques. The probability of prolonged useful survival is suggested by the fact that of the 21 patients followed for more than 1 year, 10 have been able to resume their former work, without serious difficulty, for from 1 to 20 years. Eight others have been able to lead useful lives with surmountable handicaps. One is prevented from working by serious pre-existent psychosis. Two remained incapacitated because of residual hemiplegia. Five patients have had recurrences after freedom from symptoms for periods ranging from 2 to 10 years.

Of special interest is the predominant tendency for meningeal tumors in this region to produce epileptic seizures as part of their symptomatology, and the increasing incidence of such seizures the nearer the tumor lies to the central sulcus. Twenty-one (84%) of the 25 patients entered hospital with a history of seizures. Of the 16 who were followed for prolonged periods after surgical intervention, seizures have ceased in 9 who received anticonvulsant drugs, and these patients ultimately have been able to discontinue the administration of diphenylhydantoin (Dillantin). Seven others continued to have attacks despite administration of anticonvulsant drugs, but these attacks have usually been mild and infrequent. In 4 of the 5 patients with recurrences, seizures eventually returned.

Radiofrequency Leukotomy for Relief of Pain: Coagulation of Medial Frontal White Fibers in Stages by Means of Inlying Electrodes. J. C. White, W. H. Sweet, and T. P. Hackett. A. M. A. Arch. Neurol. 2:317-330 (March) 1960 [Chicago].

The authors have developed a new conservative method of frontal leukotomy which permits relief of pain with minimal risk of psychological deterioration. This is carried out by coagulation of successive areas of the mediofrontal white matter with implanted electrodes. The employment of a continuous radio-frequency alternating current, at a power output of 32 to 40 watts, causes destruction of the brain tissue surrounding the electrode by boiling heat, with production of a zone of necrosis 10 to 15 mm. in diameter. By pulling out the electrodes 1 to 1.5 cm. at a time, the extent of destruction can be carried upward in 3 or 4 successive stages in each hemisphere with the aid of radiographic control while the patient is observed by the surgeon and psychiatrist over a period of several weeks, before the electrodes are withdrawn.

Nineteen patients with advanced malignant disease were treated by this method of radio-frequency leukotomy in conservative stages. Sixteen of the 19 patients obtained satisfactory relief, with striking reduction in the need for narcotics. Except for 2 patients who survived only briefly, there were no serious psychological complications.

The new method is proposed for the treatment of patients with advanced malignant disease in whom the lesions are too high to be treated by chordotomy, are spread over too wide an area to permit cutting the posterior sensory roots in the cervical cord or brain stem, or so far advanced that the patient cannot be subjected to any major operation.

Cerebral Hemorrhage in Leukemia. S. N. Groch, G. P. Sayre, and F. J. Heck. A. M. A. Arch. Neurol. 2:439-451 (April) 1960 [Chicago].

Cerebral hemorrhage is known to be a potential complication of leukemia, but there is little information on its incidence. Autopsies were performed at the Mayo Clinic on 235 patients with leukemia, and in 93 of these the contents of the cranial cavity were examined. Cerebral hemorrhage was found at necropsy in 46 of these 93 leukemic patients (49%). Of these 46 patients, 42 showed a picture of acute leukemia at the time of death; the leukemi in 20 of them was of the acute lymphocytic typ

Cerebral hemorrhage tended to be multiple an had a propensity for the white matter of the cerebral hemisphere. The cerebral hemispheres wer involved in 36 of the 46 patients. In 25 patient cerebral hemorrhage was the immediate cause o death. There was evidence that neurologic manifestations are more likely to be caused by hemorrhage that is ultimately fatal. The number of platelets plays an important, but not necessarily a primary, role in the causation of cerebral hemorrhag in leukemia. Extensive disturbance is present i the coagulation mechanism of leukemic patient with cerebral hemorrhage.

The authors conclude that cerebral hemorrhag is a common and often fatal complication of leukemia, and its occurs more frequently than is suspected clinically. Numerous factors play a part i causing this hemorrhage. Few of these factors ar amenable to treatment, and some are the result o treatment directed at the disease process itsel Study of microscopic sections of the brains affecte by cerebral hemorrhage in leukemic patients lead to the conclusion that the hemorrhage is not th result of leukemic infiltration but occurs because o a defect of the cerebral vasculature.

GYNECOLOGY & OBSTETRICS

Breast Cancer in Relation to Nursing and Menopausal History. B. MacMahon and M. Feinleib J. Nat. Cancer Inst. 24:733-753 (March) 1960 [Washington, D. C.].

It has been reported that the proportion of women who have never nursed a child is greater in groups of patients with breast cancer than in comparison groups. It has been suggested also that the risk of developing breast cancer is decreased by early or artificial menopause. The major difficulty in accepting these deductions is that few of the studies were adequately controlled. The purpose of the present study was to compare a group of breast-cancer patients with a group that was carefully matched with the cancer patients in respect to fertility and a number of other characteristics. Breast-cancer patients undergoing treatment or follow-up at 5 New York hospitals were interviewed. The comparison group was derived from patients attending the general surgical clinics of the same hospitals, with diseases other than cancer. There were 340 patients in each group, and the 2 groups were matched for 8 variables.

No appreciable differences between the breast-cancer patients and the comparison patients in regard to their nursing histories were observed. It is suggested that the previously reported relationships between nursing history and breast-cancer risk are explainable on the basis of variations in other intermediate variables, such as parity, age, and socioeconomic characteristics. The existence of a relationship between breast cancer and artificial menopause, postulated by previous workers, is supported by the observation that the frequency of artificial menopause was significantly lower among the breast-cancer patients than in the comparison group. This relationship is independent of fertility. No significant difference between the cancer group and the comparison patients was observed with respect to menstrual activity, fetal death, smoking history, or frequency of major illnesses and operations.

Primary Endometriosis of the Cervix. D. H. Overton Jr., R. B. Wilson, and M. B. Dockerty. Am. J. Obst. & Gynec. 79:768-778 (April) 1960 [St. Louis].

The authors report on 65 patients with primary endometriosis of the cervix. The patients' ages ranged from 24 to 53 years, and none was postmenopausal. The most common sign was vaginal spotting, bleeding, or discharge, but 46% of the patients had no abnormal bleeding or discharge, and the lesions were found during routine examinations. The lesions were not characteristic; they varied from nonspecific friable, erosive, or bleeding areas to clearly defined blue, black, or red cystic or punctate areas. Cervical trauma appeared to be an etiological factor in all but 3 patients. Cervical cautery caused 63% of the various types of trauma, the others were caused by vaginal delivery, dilatation and curettage; 1 was caused by a tenaculum. Since the incidence of cervical trauma is high, there has been occasional speculation as to the relatively infrequent occurrence of endometriosis of the cervix. Some workers expressed the view that the absence of sterile conditions, the resistance of intact squamous epithelium, and the frequent presence of some degree of infection in cervical erosions and lacerations were inhibiting factors.

Histologically, the lesions of primary endometriosis of the cervix were located superficially, with occasional ulceration through the overlying squamous epithelium. Chronic inflammation and also hemorrhage were evident in some patients. There was 1 instance of decidual reaction and 1 of pseudodecidual reaction. The microscopic examinations of the biopsy specimens showed that superficial lesions reacted to cyclic hormonal stimulation. There is much agreement, backed by clinical and experimental support, that menstrual epithelium can implant. The treatment of choice appears to be simple excision for identification followed by electrocautery. Aseptic technique, prophylactic antiseptic agents, and close observation of the patient after treatment are indicated. Primary cervical endometriosis is rarely serious or disabling, but because it produces vaginal bleeding and suspicious cervical lesions it should be diagnosed and treated.

The Genital Anomaly Associated with Prenatal Exposure to Progestogens. H. W. Jones Jr. and L. Wilkins. Fertil. & Steril. 11:148-156 (March-April) 1960 [New York].

The authors present observations on 27 female children who had masculinization of the external genitalia without progressive virilization. The mothers of 17 of these had received 17-ethinyltestosterone. Two other mothers had received 17-ethinyl-19-nor-testosterone, 2, progesterone, and 1, methyltestosterone. Three mothers had received no medication. The anatomic arrangement of the deformity was similar to that observed in congenital adrenal hyperplasia. Surgical correction was quite satisfactory, without damage to either the generative or urologic structures.

Although the masculinization of the external genitalia of the children was associated with maternal medication, the association was not a simple one. The progestogens concerned are widely used, and only a very small proportion of babies born of treated mothers are affected. Differences in hormone deficiency, placental permeability, hormone metabolism, and end-organ sensitivity are probably concerned in the effect. The question arises as to the propriety of the use of progestogens for the therapy of pregnancy wastage. It is known that some progestogens are less androgenic than others with respect to the fetal female external genitalia. Progesterone, the natural hormone, seems to give less trouble than 17-ethinyltestosterone and considerably less trouble than 17-ethinyl-19-nor-testosterone. The authors feel that the danger of this undesirable side-effect is not great enough to interdict the use of these compounds for the treatment of pregnancy wastage, but common sense suggests the use of those that have given the least trouble. Furthermore, the use of a progestogen should be reserved for women in whom a progestogenic deficiency can be shown to exist.

Significance of the Class III Cervical Smear. J. E. Hall and I. H. Rosen. Am. J. Obst. & Gynec. 79:709-717 (April) 1960 [St. Louis].

A study was made on the correlation between the cytological and histological findings in 530 patients whose cervical smears were classified as Class III. Tissue examination revealed benign lesions in 291 patients and malignant lesions in 239. In the 291 patients with benign lesions, the most frequent cytological finding was basal cell hyperplasia (48.1%), which marks the importance of this classification and lends emphasis to the contention that basal cell hyperplasia is a premalignant lesion. Of the 239 patients with malignant lesions, 207 were known to have a malignant disease, but 32 had nothing to indicate a malignant process other than a "suspicious" smear; tissue examination disclosed carcinoma in situ in 24 of these, invasive cancer in 5, and adenocarcinoma of the endometrium in 2. The age distribution for all patients ranged from 10 to 80 years. It is of interest that the median age for the patients with basal cell hyperplasia was 25 years, and for those with carcinoma of the cervix was 41 years. Thus, basal cell hyperplasia usually occurs at an earlier age than carcinoma of the cervix and may indicate its role as a forerunner of carcinoma.

Hand-Schüller-Christian Disease and Pregnancy: Report of a Case. D. B. Heilbronn and D. N. Rigway. Am. J. Obst. & Gynec. 79:805-809 (April) 1960 [St. Louis].

The occurrence of a successfully terminated pregnancy in a 20-year-old woman with Schüller-Christian disease is reported which apparently represents the 1st such case recorded in literature. The authors present a brief review of Schüller-Christian disease, the classical triad of which is multiple defects in membranous bones, exophthalmos, and diabetes insipidus. A commentary on the incidence of diabetes in pregnancy, its course and management are also included.

PEDIATRICS

Pertussis: A Clinical Study. S. Kaufman and H. B. Bruyn. A. M. A. J. Dis. Child. 99:417-422 (April) 1960 [Chicago].

The authors reviewed the records of 199 patients with pertussis admitted to the San Francisco General Hospital between 1947 and 1958. All children under 1 year of age with pertussis were admitted to the hospital regardless of the severity of their symptoms; many of the older children were hospitalized because of complications. Of the patients admitted, 113 (57%) were in the 1st year of life and 78 of these were less than 6 months old. Immunization had been instituted in 31 patients prior to the onset of symptoms, but in only 13 had it been completed. It is possible that a few cases of parapertussis were included in this series because the 2 diseases are clinically indistinguishable, although the symptoms of parapertussis are generally milder and of shorter duration. There is no cross immunity between the diseases, and pertussis vaccine affords no protection against parapertussis.

Contact within the home is the most important means by which pertussis is acquired. The neonate can be best protected by adequate primary immunization or booster inoculation of siblings during the maternal gestation period. Therapy during the catarrhal stage is somewhat efficacious, but, in the absence of a history of contact, the diagnosis is difficult to establish during this early stage. White blood cell count may be suggestive, but it is not helpful in dismissing the diagnosis. Paroxysmal cough, emesis, and coryza are seen in the majority of patients. Therapy during the paroxysmal stage does not often alter the clinical course and may not prevent secondary bacterial complications. Nevertheless, in the critically ill and in the infant, antibiotics and hyperimmune human globulin are given in the hope that the paroxysmal stage will be shortened.

A Study of Children with Mongolism Reared in the Home Compared to Those Reared away from the Home. S. A. Centerwall and W. R. Centerwall. Pediatrics 25:678-685 (April) 1960 [Springfield, Ill.].

A comparison was made of the physical and mental development of children with mongolism who were put into foster homes very soon after birth (group P) with that of similar children who were reared in their own homes until 2½ years of age or older (group H). All of these children at the time of study had been patients at a state hospital for several years. The two groups (32 children each) were matched as to age but were otherwise, chosen in a random way from the hospital population.

The children of group H showed significantly better nutrition and growth and walked at a much earlier age. The average intelligence quotient of group P children at an average age of 7 years was 16; that of group H at the same age was 23. The social quotients at the same ages were 24 for group P and 32 for group H. A statistical analysis of these differences shows them to be highly significant. The children in group P usually functioned within the severely-retarded range, whereas those in group H were within the moderately retarded or trainable range. The authors concluded that the average baby with mongolism has a better chance of being a happy, easily cared for, somewhat productive person, if a reasonable adjustment can be made to having him remain in his own home during the first years of life.

Studies in the Relationship of Amino Acids to Infantile Hypoglycemia. W. A. Cochrane. A. M. A. J. Dis. Child. 99:476-488 (April) 1960 [Chicago].

Spontaneous hypoglycemia is not a disease but an indication of a defect in the sugar metabolism. The author and his collaborators had observed in 1956 that some hypoglycemic infants had more frequent hypoglycemic attacks when they were treated with a high protein diet. That protein aggravates some cases of infantile hypoglycemia was supported by the finding of a marked fall in blood sugar content in 3 patients after the administration of the amino acid L-leucine. This particular amino acid was selected partly because it had been reported that glucose administration to normal men results in a fall in blood amino acid, leucine being depressed more than other amino acids. In part 1 of this report the author describes observations made in 12 hypoglycemic infants and children after the oral administration of various amino acids. Six of the patients investigated revealed a marked fall in blood sugar after the administration of casein hydrolysate or L-leucine. The leucine-sensitive patients were tested with several other amino acids without evidence of a similar hypoglycemic effect. After these observations on hypoglycemic children, the hypoglycemic effect of L-leucine was investigated in animals, and these studies are described in part 2.

In vivo animal experiments included the intravenous administration of L-leucine to rabbits, rats, and dogs. In vitro experiments with use of isolated rat diaphragm indicated an increased uptake of glucose in the presence of L-leucine. Insufficient experiments have been carried out with rat liver slices to interpret the results, but it appears that leucine may also interfere with some metabolic process in the liver. Possible biochemical explanations of the hypoglycemic effect of leucine are presented, with a review of the pertinent literature. Finally the therapy of infantile hypoglycemia is discussed, and it is suggested that the administration of cortisone or corticotropin combined with extra carbohydrate 30 minutes after feeding is the therapy of choice. A low leucine diet might be considered for the treatment of hypoglycemic patients who are found to be markedly sensitive to leucine.

The Prompt Treatment of Salicylism with Sodium Bicarbonate. T. K. Oliver Jr. and M. E. Dyer. A. M. A. Dis. Child. 99:553-565 (May) 1960 [Chicago].

Thirty-eight children (14 to 48-months-old) with acute salicylism were treated with fluids and sodium bicarbonate. Twelve children received and retained fluids given orally or intravenously in amounts above 3 liters per square meter daily. Most of these 12 patients also received an intravenous infusion of 0.3% sodium chloride in 6.6% dextrose solution; a few received a polyionic solution with 5% of fructose. Eighteen children received, besides the fluid regime, sodium bicarbonate given intravenously (3.5 to 5.0 mEq. per kilogram) during the initial 4 hours of treatment. Eight children received and retained less than 2.5 liters of fluid per square meter per day. The patients received an emetic by mouth before starting the therapy. Bicarbonate administration was followed by excretion of an alkaline urine and fall in serum salicylate in 15 of the 18 children receiving sodium bicarbonate intravenously. This fall was more gradual in the 2 groups who received only fluids. No complications were observed. The rapid fall of serum salicylate levels suggests that careful use of sodium bicarbonate is the preferred treatment of salicylism in children under 4 years of age. Urine pH concentration should be determined frequently and additional bicarbonate given if the urine does not become alkaline within 4 hours after starting the therapy.

Staphylococcal Pneumonia: A Review of 329 Cases. A. W. Rebhan and H. E. Edwards. Canad. M. A. J. 82:513-517 (March 5) 1960 [Toronto].

Histories of patients with staphylococcic pneumonia treated between 1950 and 1958, were reviewed in order to ascertain the best method of treatment, one followed by the lowest mortality. Included were all patients with roentgenologically proved pneumonia suggestive of the staphylococcic variety and in whom the presence of pyogenic staphylococci were proved by means of cultures made from material obtained either by auger suction, thoracentesis, bronchoscopic suction, postmortem removal or from blood. During this nine-year period 329 cases of staphylococcal pneumonia were treated. The attack rate was somewhat higher in boys than in girls. Of all cases in the group, 68% were under 1 year of age. Forty-seven children died and autopsies were performed. Thirty-nine of the 47 deaths (83%) occurred in infants less than 1 year old. Thirty-five of the 47 children who died had had contact with a hospital during the 6 weeks before the onset of pneumonia. Mortality was highest in 1953, when 8 of 13 children died (61.5%); and lowest in 1958, when there were 7 deaths among 78 patients (8.9%). The presence of a strain sensitive to all antibiotics does not necessarily guarantee a good prognosis; in 12% of the fatalities staphylococci sensitive to penicillin had been proved. However, the dramatic drop in mortality from 61.5% in 1953, to 11.6% in 1954 has to be attributed to the use of more appropriate antibiotics such as chloramphenicol and erythromycin. Only a small percentage of strains have shown resistance to these 2 antibiotics, and none to bacitracin. This latter drug was used intramuscularly in a few patients who were seriously ill, with excellent results and without any evidence of nephrotoxicity. Early and adequate drainage of the chest, and bronchoscopy where necessary, are also prime requisites of successful treatment.

Cor Biloculare: Report of 3 Cases. H. W. Hyatt Sr. Arch. Pediat. 77:165-170 (April) 1960 [New York].

Of the 3 infants whose histories are presented 2 were boys and 1 was a girl. All 3 exhibited cyanosis and respiratory difficulties and died when they were less than 3 days old. Postmortem examination revealed that the heart had only 2 chambers.

Cor biloculare is one of the rarest cardiac lesions, and it is rarely suspected. It was considered in only 1 of the 3 cases. There is nothing in the history, physical examination, or chest roentgenogram that will enable one to make an unequivocal diagnosis of this condition. Although cor biloculare is not usually compatible with life, the literature reports 1 patient with cor biloculare and transposition of the great vessels, who lived for 27 years and 3 months, while another patient with cor biloculare and persistent truncus arteriosus lived for 36 years and 2 months. In very young infants with signs of heart disease cor biloculare should be considered, unless the infant has some definite indications of a specific type of heart disease, such as lower blood pressure in the legs than in the arms as seen in coarctation of the aorta, or the machinery murmur in patent ductus arteriosus, etc.

ENDOCRINOLOGY

ACTH-Producing Pituitary Tumors Following Adrenalectomy for Cushing's Syndrome. D. H. Nelson, J. W. Meakin, and G. W. Thorn. Ann. Int. Med. 52:560-569 (March) 1960 [Lancaster, Pa.].

The authors report on 10 patients who were admitted to the Peter Bent Brigham Hospital, Boston, and in whom evidence of a disturbance of the pituitary gland was observed after a previous bilateral adrenalectomy for adrenal cortical hyperfunction (Cushing's syndrome). All of these patients showed deep generalized pigmentation. In 8 patients a tumor of the pituitary gland was revealed by roentgenologic examination, and restricted visual fields or both. In 2 patients, markedly elevated plasma-ACTH levels were found in association with deep pigmentation, but no tumor of the pituitary gland was demonstrable. In 5 of the 10 patients a plasma-ACTH level was determined which was above that usually observed in patients with adrenal cortical hypofunction (Addison's disease), or in those in whom a bilateral adrenalectomy has been carried out. All 5 patients who did not have elevated levels of plasma-ACTH, but who had deep pigmentation, and who did have evidence of pituitary tumors after adrenalectomy for Cushing's syndrome, had received irradiation to the pituitary gland before the time that the first plasma specimen was obtained for ACTH assay.

The average time from adrenalectomy to the appearance of the pituitary tumor was 3 years, with a range of from 1 to 8 years, and in 2 patients from whom pituitary tissue was removed surgically, the histological examination revealed the presence of tumor cells of a "chromophobe type." Although in none of the 10 patients was there evidence of a tumor of the pituitary gland before the bilateral adrenalectomy, the possibility cannot be ruled out that a very small tumor was present which might have been responsible for the development of Cushing's syndrome in these patients. It seems that this tumor subsequently may have grown to a larger and more easily demonstrable size after the adrenalectomy and that it then excreted increased amounts of ACTH. The increased pigmentation might have been due to the effect of the melanin-stimulating activity within the ACTH molecule and, perhaps, of a concomitant increase of the secretion of melanin-stimulating hormone by the pituitary tumor.

The Diuretic Response to Administered Water in Patients with Primary Myxedema. K. H. Bleifer, J. L. Belsky, L. Saxon, and S. Papper. J. Clin. Endocrinol. 20:409-414 (March) 1960 [Springfield, Ill.].

Although impairment of ability to obtain a brisk diuresis following administration of water has been clearly demonstrated in patients with hypopituitarism and secondary myxedema, the data with regard to primary myxedema are less well defined and are somewhat contradictory. Eight patients with classic, untreated primary myxedema were studied. Isotonic hexose solution (20 ml. per kilogram of body weight) was administered intravenously within a one-hour period to each of these patients when they were normally hydrated and recumbent. Urine specimens were collected at approximately half-hour intervals until maximal rates of urine flow were achieved. On another occasion, 7 of the 8 patients were given a similar quantity of tap water orally. Venous blood was obtained at the height of diuresis and at the end of the study. Urine and blood were analyzed for sodium, potassium, and chloride contents, creatinine clearance, and total solute level.

The maximal rate of urine flow was definitely reduced below the normal range (minimum, approximately 8 ml. per minute) in 2 of the 8 patients. In each of 5 patients restudied after treatment with desiccated thyroid, including 3 whose pretreatment peak flow of urine was greater than 8 ml. per minute, there was an increase in maximal diuretic response. The urine, during periods of maximal flow after treatment, was more dilute than before treatment in 4 of these patients. The rate of total solute or sodium excretion did not bear a consistent relationship to increased urine flow. Endogenous creatinine clearance increased significantly after treatment in all 5 patients. The authors feel that the modest limitation in water diuresis observed in primary myxedema may be attributed to a reduction in glomerular filtration rate. The diuretic response to water is a useful test to differentiate primary myxedema from panhypopituitarism with secondary myxedema.

DERMATOLOGY

Psoriasis and Arthritis. W. B. Reed and S. W. Becker. A. M. A. Arch. Dermat. 81:577-585 (April) 1960 [Chicago].

The authors carried out clinical and laboratory studies on 29 men and 11 women with psoriasis and arthritis who came from the Long Beach Veterans Administration Hospital, the Los Angeles General Hospital, the White Memorial Hospital, and from private practices of rheumatologists and dermatologists in California. Roentgenographic studies and clinical photographs were made whenever possible, with emphasis on the bony changes of the hands and feet, the sites most involved in psoriatic arthritis. Although the arthritis may resemble rheumatoid when the larger joints are involved, psoriatic arthritis is a distinct clinical entity, particularly when the terminal interphalangeal joints are involved. The predominance of cases in men, the absence of rheumatoid nodules, the asymmetrical joint involvement, and the massive bone destruction, are different from classic rheumatoid arthritis. The close association between the severity of the arthritis and the cutaneous manifestation is important, with emphasis on the higher incidence of pustular psoriasis and psoriatic erythroderma.

The failure of the latex fixation tests to reveal the rheumatoid factor is another important difference between rheumatoid and psoriatic arthritis. Only 5 of the 40 patients had positive titers from these tests. Of the 5 patients with positive results from the tests, only 1 showed definite psoriatic arthritis. He may have had a false positive reaction, as is found sometimes in other hypergammaglobulinemic states. The therapy of this arthritis is for the most part ineffectual. The administration of corticosteroids may improve the symptoms of arthritis, but seems to have little effect on the psoriasis.

Diffuse Alopecia in Women: Its Unexplained Apparent Increase in Incidence. M. B. Sulzberger, V. H. Witten, and A. W. Kopf. A. M. A. Arch. Dermat. 81:556-560 (April) 1960 [Chicago].

A questionnaire was sent to 170 members of the American Dermatological Association in an attempt to find out whether the authors' observation of a noticeable increase in the number of their female patients complaining of diffuse loss of hair of the scalp was limited to their practice or whether other dermatologists had seen similar increases in the incidence of this complaint. The questionnaires were answered and returned by 106 dermatologists (62%). Fifty-six dermatologists (53% of those who replied) reported an increase; 32 (30%) did not observe any increase, and 16 (15%) were not sure that they had noted such a change. Two left the question blank. The authors' observation in their private practice during the last 5 years of a sharp increase in diffuse alopecia of the scalp in female patients past the age of puberty was shared with over one-half of the 106 experienced dermatologists of North America who answered the questionnaire. Dermatologists in certain European countries have similarly observed a sharply increased incidence of female balding. The etiology, pathogenesis, and therapy of this female balding are unknown.

UROLOGY

Athlete's Kidney. A. H. Kleiman. J. Urol. 83:321-329 (April) 1960 [Baltimore].

Eleven hundred athletes were examined urologically during a 4-year study for the effect of chronic trauma and strenuous exercise on renal morphology. Preactivity hematuria and proteinuria were found in approximately 8% of the boxers; postfight hematuria was present in 65%, and postfight proteinuria in 67%. Postexercise urinalyses were performed on 900 boxers, 140 wrestlers, 68 basketball players, and 30 hockey players who participated in events in New York City. A common finding in all groups was the presence of protein, red blood cells, white blood cells, and casts. One hundred twenty-five boxers and 20 wrestlers with abnormal urinary sediments were subjected to urography, while 27 boxers with normal urinalyses served as a control group. Repeated urographic studies of 86 subjects showed distortions of the upper urinary tract frequently associated with congenital anomaly, ptosis or hydronephrosis. Parenchymal changes, suggesting athlete's kidney, tended to appear most often around the upper calyx of the right kidney. Abnormal morphologic patterns involving the right upper calyx were found in 44% of the urograms taken on 125 professional pugilists.

Direct body trauma by blows, indirect trauma associated with frequent crouching, and marked physical exertion are the main factors in the etiology of athlete's kidney. Treatment includes an adequate period of rest, and evaluation of follow-up urinalyses and urograms. Surgical intervention or prolonged medical treatment is rarely necessary.

Premarin Intravenous in Prostatic Surgery. C. K. Bobelis. Illinois M. J. 117:231-232 (April) 1960 [Chicago].

A conjugated estrogenic substance (Premarin) was administered by intravenous injection to control the tendency to excessive hemorrhage in patients undergoing prostatectomy. The 80 patients in whom the hemostatic effect was studied underwent one of the following 4 prostatic operations:

suprapubic, retropubic, or perineal prostatectomy, or a transurethral resection. The last operation was carried out in more than half of the patients. In 18 of the patients pathologic studies revealed carcinoma, and the remaining 62 had benign prostatic hypertrophy. Thirty of the 80 patients (group 1) were given intravenous injection of conjugated estrogenic substance postoperatively, 30 before operation (group 2) and the remaining 20 patients (group 3) served as controls.

The results in group 1 indicated that intravenous injection of conjugated estrogenic substance is an effective, practical, and safe method of controlling excessive postoperative bleeding, the urine clearing in 24 hours after injection in 28 of the 30 cases. The results in group 2 indicate that the administration of Premarin Intravenous the evening before operation reduced bleeding to a minimum during surgery and facilitated the operative technique in transurethral resection. In open surgery on the prostate, the administration 1 to 2 hours preoperatively did not give as good results as administration 15 to 18 hours before surgery. On the basis of these results, the author believes that the administration of 20 mg. of Premarin Intravenous the evening before operation will in most cases help control excess bleeding associated with prostatic surgery, particularly in the transurethral resection.

OTOLARYNGOLOGY

Radiation Necrosis of the Ossicles. J. Gyorkey and F. J. Pollock. A. M. A. Arch. Otolaryng. 71:793-796 (May) 1960 [Chicago].

The patient presented here was a 17-year-old youth, who complained, in 1958, of progressive hearing loss in the right ear since 1953. In 1951, the patient had received a total dose of 9,900 r to the head for an ependymoblastoma of the floor of the fourth ventricle. It has been previously shown that radiation of bone over a long period causes vascular changes. The vascular supply of the long process of the incus is known to be fairly meager. The hearing loss that developed was of a conductive type, consistent with interruption of the ossicular chain or fixation of the stapes. Surgical exploration revealed that the long process and the lenticular process of the incus were replaced by a fibrous band. This could have been the end-result of an aseptic necrosis due to the radiation effect on the vascular supply of the long process of the incus. Hearing was restored to a useful level in the speech frequencies by means of a myringostapediopexy.

Disappearance of the long process and lenticular process of the incus has been found at surgery in the presence of chronic otitis media, with or without the formation of cholesteatoma. The absence of these processes has been also reported many years after a skull fracture with injury of the temporal bone; and congenital malformation of the ossicles frequently has been recorded in the literature. However, destruction of the incus due to massive radiation has not been previously reported.

Mediastinal Emphysema Complicating Tracheotomy. O. Bergstrom and H. Diamant. A. M. A. Arch. Otolaryng. 71:628-634 (April) 1960 [Chicago].

Mediastinal emphysema may develop as a complication of tracheotomy. The chief cause of this complication seems to be the increase in negative intrathoracic pressure brought about by respiratory obstruction which results in the intake of air at the tracheotomy procedure itself. The most critical step in the operation is the incision of the pretracheal fascia, since air appears most readily to be drawn in between this fascial plane and the trachea. Hemorrhage and other technical difficulties prolonging the operation also add to the danger of this type of complication. It appears that the emphysema must attain a certain massiveness before it affects respiration or circulation, and the mildness of the symptoms in many cases may be the reason why mediastinal emphysema has escaped detection as a complication of tracheotomy. The authors made studies of 465 infants and children with acute laryngitis (pseudocroup) observed during the decade 1949 to 1958, at the Department of Otolaryngology, Karolinska Sjukhuset, Stockholm. Tracheotomy was performed in 55 of these 465 patients and also in 19 children who did not have acute laryngitis but had respiratory obstruction, or in whom bronchoscopy or operation was to be facilitated.

The authors base the discussion of mediastinal emphysema complicating tracheotomy on 5 illustrative case histories and on literature reports. They found that pneumothorax complicates tracheotomy less frequently than does mediastinal emphysema. Twenty-eight of the 55 tracheotomized pseudocroup patients were examined roentgenographically. Twenty-two of these 28 children were found to have more or less extensive mediastinal emphysema, and 6 of these 22 also had pneumothorax. Among the 19 tracheotomized patients not suffering from pseudocroup, mediastinal emphysema was noted only in cases in which the operation was indicated by respiratory obstruction. This group comprised 5 children, in 3 of whom mediastinal emphysema developed. Tracheotomy in cases without respiratory obstruction (so-called elective tracheotomy to facilitate bronchoscopy or operation) was not complicated by mediastinal emphysema.

Intubation has been recommended to prevent the development of mediastinal emphysema. The authors found that intubation did not always prevent mediastinal emphysema, while a number of tracheotomies not preceded by intubation ran a wholly uneventful course. Attempted intubation may waste valuable time when a free airway must be secured quickly. There should be no hesitation in performing early or emergency tracheotomy without prior intubation.

INDUSTRIAL MEDICINE

Farmer's Lung: Report of 2 Cases. W. P. Baldus and J. B. Peter. New England J. Med. 262:700-705 (April 7) 1960 [Boston].

The authors report on 2 patients who exhibited the clinical, roentgenologic, and pathological features of farmer's lung. Biopsy of the lung was obtained in both cases, and in 1 of the patients the symptoms were reproduced by deliberate exposure to dust during the period of study. The patients were 2 farmers aged 39 and 45 years respectively, whose 1st symptom was an intermittent attack of dyspnea later accompanied by cough, fever, chills, malaise, and weight loss. One patient related the onset of the disease to exposure to dust of moldy hay, while the other had experienced an acute onset after being exposed to dust for 2 years. In both patients Candida albicans was isolated from sputum cultures, and the only physical finding was the presence of diffuse crepitant inspiratory rales. X-ray examination of the chest showed a diffusely reticular and finely nodular bilateral pattern. Sections of the lung biopsies revealed many peribronchiolar granulomas in which giant cells were the predominant feature.

The fact that in 1 of the patients the inhalation of dust of moldy hay during his stay in the hospital brought about a recurrence of symptoms lends support to the hypothesis that farmer's lung is a hypersensitivity reaction. Farmer's lung and silo-filler's disease seem to be distinct entities caused by separate agents, although there are probably mild forms of both diseases which cannot be identified as either syndrome.

Human Inhalation Anthrax: A Report of 3 Fatal Cases. W. S. Albrink, S. M. Brooks, R. E. Biron, and M. Kopel. Am. J. Path. 36:457-468 (April) 1960 [Ann Arbor, Mich.].

During a 10-week period in 1957, autopsies performed on 3 textile workers from Manchester, N. H., revealed disseminated infection with Bacillus anthracis as the cause of death. During this time 4 nonfatal cases of cutaneous anthrax and 2 other suspected but unproved cases of inhalation anthrax were observed. The present report is concerned with pathologic findings in the 3 fatal cases. Two of the 3 patients showed massive hemorrhagic mediastinitis; 1 of these and the 3rd patient were found to have hemorrhagic meningitis. Other secondary manifestations were hemorrhagic thyroiditis in 1 patient and ulcerations of the ileal mucosa in another. In each instance the onset was insidious, the clinical manifestations were obscure, and the course of the disease was fulminating. Recognition of anthrax is extremely difficult and the diagnosis is rarely made prior to death.

The observed pathologic alterations support the following conclusions regarding pathogenesis, based in turn on previously reported experimental work: (1) anthrax spores contained in small particles (5μ or less) are deposited in alveoli where phagocytosis by large mononuclear cells is followed by transport across alveolar walls to regional lymph nodes via lymphatic channels; (2) although germination of some spores may occur en route, maturation usually eventuates after deposition in lymph nodes; multiplication of vegetative forms results in necrosis and hemorrhage in the nodes, and organisms may spread directly to contiguous structures (mediastinum and the walls of the trachea and bronchi); (3) septicemia and dissemination of either spore-containing macrophages or vegetative forms result in such secondary manifestations as edema, hemorrhage, meningitis, or ulceration in the alimentary tract.

THERAPEUTICS

Tolbutamide-Induced Improvement in Carbohydrate Tolerance of Young People With Mild Diabetes Mellitus. S. S. Fajans and J. W. Conn. Diabetes 9:83-88 (March-April) 1960 [New York].

The effect of therapy with tolbutamide on carbohydrate tolerance of 14 nonobese patients with mild, asymptomatic diabetes mellitus has been investigated. The ages of the patients ranged from 11 to 35 years. Tolbutamide was given in a dosage of 0.5 Gm. twice daily. Diets used in conjunction with the drug contained 225 to 250 Gm. of carbohydrate and maintenance calories. Glucose tolerance tests were repeated at intervals of 2 to 4 months for as long as 27 months after the beginning of therapy.

Results indicate that over the short period of time covered by this study, carbohydrate tolerance of young patients with mild asymptomatic diabetes may be greatly improved under the influence of tolbutamide. Improvement in varying degrees occurred in all the patients. Findings indicate that dietary changes by themselves were not responsible for the improvement in glucose tolerance. Tolbutamide was administered for from 3 to 13 months before improvement or normal carbohydrate tolerance could be demonstrated. More extensive studies of the patients reported on are needed to determine whether prolonged treatment with sulfonylureas can prevent decompensation of islet cell function in young mildly diabetic patients. It is assumed that there was preservation of normal islet cell tissue in most of the patients in this series, since they were asymptomatic when diabetes was detected. Normalization of the response to a glucose load as well as occurrence of fasting and postprandial hypoglycemia suggest increased insulin secretion as a mode of action of tolbutamide in these patients.

Increased Transmissibility of Staphylococci to Patients Receiving an Antimicrobial Drug. C. A. Berntsen and W. McDermott. New England J. Med. 262:637-642 (March 31) 1960 [Boston].

Transmissibility of staphylococci to patients receiving an antimicrobial drug has been studied in 294 patients admitted to the same ward of Bellevue Hospital, New York. One hundred thirty of the 294 patients received no treatment and served as controls; 120 patients were given tetracycline, generally by mouth, in doses of 250 mg. 4 times daily for a period of about 11 days. The remaining 44 patients received systemic therapy with antimicrobial drugs other than tetracycline before or during their residence on the ward.

On admission to the hospital, 86 untreated and 79 treated patients from the 2 groups (130 untreated and 120 tetracycline treated) were not demonstrable nasopharyngeal carriers of staphylococci. The carrier state developed in 15 of the 86 patients in the untreated group and in 36 of the 79 patients in the treated group during the first 4 weeks in the hospital. New strains were substituted for old in 12 of the 44 original carriers of the untreated group and in 24 of the 41 original carriers in the tetracycline group. Thus a new strain of staphylococci was acquired in 29% more of the group of patients who received tetracycline than among those who received no antimicrobial therapy. In 56 of the 60 treated patients who acquired new strains of staphylococci while in the hospital, the new strains were drug resistant whereas the newly acquired strains of staphylococci were drug resistant in only 10 of the 27 patients who received no antimicrobial therapy. New strains of staphylococci were acquired by 16 of the 44 patients receiving antimicrobial therapy other than tetracycline; 1 patient acquired 2 strains. In 10 patients the acquisition represented a substitution of 1 strain for another. Of the 19 strains acquired, 12 were drug resistant.

Analysis of the obtained data yielded no significant evidence in either support or denial of the possibility that a drug-induced change in the microbial flora plays a part in the increased transmissibility of the staphylococci to the drug-treated patients. It is believed that an important factor in this increased transmissibility of the staphylococci to the treated patients was the drug-induced interference with the usual interspecies relations among the nasopharyngeal flora.

Effective Plan for Control of Pruritus Ani. H. D. Trimpi. Dis. Colon & Rectum 3:125-129 (March-April) 1960 [Philadelphia].

Trimeprazine (Temaril), a phenothiazine compound, was administered orally to 39 men and 17 women aged from 21 to 73 years, with pruritus ani. The perianal area of most of the patients was inflamed and severely excoriated. Fifty-three of the 56 patients had been previously treated without success with steroids, surgical procedures, irradiation, or other methods of therapy. The average daily dose of trimeprazine given was 10 mg. Forty-five patients, including those previously receiving steroid medication, were given triamcinolone acetonide and were instructed to apply it locally 3 or 4 times daily. Other topical application of palliative creams and lotions was continued in 6 patients. Dosage adjustment of all medication was made weekly in accordance with the patient's response. After a week, and occasionally after 2 weeks of this type of therapy, when symptoms were controlled, administration of triamcinolone was gradually reduced and/or discontinued. Duration of therapy for the entire group ranged from 3 to 15 weeks.

Complete relief from itching was obtained by the combined use of trimeprazine and local application of steroids in 37 patients, and partial relief in 10; the latter patients obtained complete relief from itching at night when the bedtime dose of trimeprazine was doubled. Of the 46 patients whose pruritus was controlled while receiving trimeprazine and local steroid therapy, 28 were able to discontinue steroid medication within 3 weeks, a shorter period than usual with drugs of this type. In most patients 6 weeks of therapy, giving trimeprazine and triamcinolone acetonide in the 1st week or two, and trimeprazine alone for the next 4 or 5 weeks, brought about cessation of the "itch-scratch" cycle. Once this cycle was broken, it was found that most patients were relieved and there was no recurrence.

Observations on the Effects of Alkylating Agents in Human Neoplastic Disease. B. E. Hall, F. M. Willett, and D. R. Hales. Ann. Int. Med. 52:602-625 (March) 1960 [Lancaster, Pa.].

The authors studied the effect of alkylating agents, namely, nitrogen mustards, ethylenimines, and sulfonic acid esters, on malignant diseases of the hemopoietic system, such as leukemia and malignant lymphoma, and on neoplastic "solid" tumors in patients treated at the San Francisco Veterans Administration Hospital. In a 12-year-old girl with far-advanced Hodgkin's disease, exceedingly good control was obtained with intermittent chlorambucil (Leukeran) therapy. A total dose of 3.4 Gm. of the drug was administered over a period of 21 months without causing serious injury to hemopoiesis. During most of this period the patient led a normal, active life despite roentgenographic evidence of residual disease in the lungs.

Remarkable regression of metastatic lesions of undifferentiated carcinoma in the parenchyma of both lungs was observed in a 56-year-old woman after a single intravenous injection of mechlorethamine (HN_2) and the oral administration of chlorambucil over a period of 10½ months. Thereafter, the pulmonary lesions were controlled with intermittent chlorambucil therapy and irradiation until evidence of extrapulmonary metastasis was noted almost 3 years after the institution of therapy. During the greater part of this three-year period the patient was asymptomatic and led a normal, active life. The intraperitoneal instillation of triethylene melamine, followed by the intravenous administration of N, N′, N″=Triethylene thiophosphoramide (Thio-Tepa) seems to have prevented the reaccumulation of ascites for a period of 10 months in a 25-year-old woman with ovarian carcinomatosis. Serial injections of Thio-Tepa directly into an infiltrating transitional cell carcinoma of the urinary bladder of a 65-year-old man, with hyaluronidase used simultaneously as a spreading agent, resulted in complete disappearance of the tumor within a period of about 3 years. Objective signs of recurrence have not as yet reappeared. A 67-year-old woman with metastases to the parenchyma of both lungs and to the right hilar and left inguinal lymph nodes, originating from a recurrent anaplastic transitional cell carcinoma of the urinary bladder, has been free of clinical evidence of the disease for a period of 1 year after a sustained course of treatment with Thio-Tepa administered intravenously.

Demethylchlortetracycline Therapy in Pneumonia, Scarlet Fever, and Other Infections. E. A. Lichter, S. Sobel, H. W. Spies, and others. A. M. A. Arch. Int. Med. 105:601-606 (April) 1960 [Chicago].

Demethylchlortetracycline (DMCT) is a new tetracycline analogue, which is produced by a mutant strain of Streptomyces aureofaciens. The authors report their experiences with this antibiotic in the treatment of 170 patients who were hospitalized with various types of infections. Of 29 patients treated for pneumococcic infections, 15 had a prompt response to therapy. In the group of 13 patients with a delayed response, 3 had developed pleural effusion before the beginning of therapy, 4 were preterminal and died from underlying neoplastic disease, and the remaining 6 patients became afebrile 4 to 9 days after onset of therapy. Of 42 children with scarlet fever, 32 were afebrile 48 hours or less after starting therapy, and all recovered. Among the other 99 patients who had various types of infections, the response was, in general, similar to that observed when the other tetracyclines are administered.

On doses of 150 mg. at 6-hour intervals or less, only 2% of the patients had slight, easily-reversible vomiting and diarrhea or both. On doses of 250 mg. every 6 hours, similar symptoms developed in 12%, and on doses of 500 mg. or more, in 61%. Since therapeutic results with the lowest doses were as good as those observed with the other tetracyclines, these doses are recommended and should cause as few, or fewer, side-reactions as full doses of any of the other tetracyclines.

The Comparison of 6-Mercaptopurine with the Combination of 6-Mercaptopurine and Azaserine in the Treatment of Acute Leukemia in Children: Results of a Cooperative Study. R. M. Heyn, C. A. Brubaker, J. H. Burchenal, and others. Blood 15:350-359 (March) 1960 [New York].

In order to facilitate clinical trials of new antileukemic drugs, the Leukemia Chemotherapy Cooperative Study Group A was organized under the Clinical Studies Panel of the Cancer Chemotherapy National Service Center. Study Group A included investigators from 11 institutions in the United States. The authors report the results of a study to determine whether or not the addition of O-diazoacetyl-L-serine (Azaserine) to 6-mercaptopurine is of value in the treatment of acute leukemia in children. O-diazoacetyl-L-serine is an antibiotic isolated from a culture broth of Streptomyces, and its mode of action appears to be that of a glutamine antagonist by inhibiting the donation by glutamine of an amino group in the conversion of formylglycinamide ribotide to formyl-glycine amidine ribotide. O-diazoacetyl-L-serine was shown to be relatively ineffective as an antileukemic agent when used alone in the treatment of acute leukemia in children.

The patients with acute leukemia chosen for study were previously untreated and were 14 years of age or under. Of 250 leukemic children seen by the investigators, 82 were not included in the study because of previous antileukemic treatment, a need for initial steroid therapy, death before any therapy could be started, or the inability of the patient to return for continued care. Of the remaining 168 children, 43 were excluded either because their condition required steroid therapy or because they died or did not return for care. The 125 patients who remained were treated for over 4 weeks. The dosage for both 6-mercaptopurine and O-diazoacetyl-L-serine was 2.5 mg. per kg. of body weight daily by mouth. When 6-mercaptopurine was used alone (in 67 patients) it was given continuously for at least 4 weeks unless the patient's condition deteriorated during that time and other therapy was deemed advisable. When the combination of drugs was given, (58 patients) it was managed in a similar way. If mouth lesions occurred, the dosage of O-diazoacetyl-L-serine was halved or stopped temporarily for 2 or 3 days.

Complete remissions resulted in 30 of the patients treated only with 6-mercaptopurine and in 28 of those treated with the combination of drugs. The percentages of partial remissions and of failures also were similar in the two groups. Furthermore the duration of the remissions obtained with the combined therapy was not significantly longer than when 6-mercaptopurine was used alone.

An Evaluation of Chemotherapy in Pulmonary Tuberculosis: High Doses of Isoniazid and PAS versus Daily Streptomycin with High Doses of Isoniazid and PAS. S. J. Berte and C. D. Bowen. Am. Rev. Resp. Dis. 81:407-411 (March) 1960 [New York].

This study was designed to observe the effectiveness of treatment employing high doses of isoniazid with para-aminosalicylic acid (PAS) in comparison with large doses of isoniazid with daily doses of both streptomycin and PAS. Patients selected for study had moderately or far advanced pulmonary tuberculosis and had received either no previous chemotherapy or chemotherapy for less than 2 months. Large doses of isoniazid, PAS, and pyridoxine were given to 113 patients with moderately and with far advanced, bacteriologically proved, active pulmonary tuberculosis. Ninety-two other patients were treated daily with streptomycin, in addition to large doses of isoniazid, PAS, and pyridoxine. The concentrations of biologically active free isoniazid found in the blood were considered adequate in the majority of the 205 patients.

It was found that when large doses of isoniazid with PAS are used in the treatment of pulmonary tuberculosis, and when adequate concentrations of free isoniazid are obtained in the blood, the use of streptomycin daily for 90 days in addition to the other drugs does not provide any significantly superior therapeutic results. Seven patients excreted tubercle bacilli which were noted to be resistant to 1 or more drugs. Despite these findings, all 7 patients experienced very satisfactory response to treatment and early reversal of infectiousness.

Pyrazinamide and Isoniazid Used in the Treatment of Pulmonary Tuberculosis. J. H. Matthews. Am. Rev. Resp. Dis. 81:348-351 (March) 1960 [New York].

The use of pyrazinamide in the treatment of pulmonary tuberculosis has been the subject of extensive studies by the Veterans Administration-Armed Forces investigators of the chemotherapy of tuberculosis since the drug was first reported as a tuberculostatic agent in January, 1952. By 1956 it appeared that perhaps the combination of pyrazinamide with isoniazid was a more effective therapeutic agent than any of the double-drug agents using isoniazid, para-aminosalicylic acid (PAS), or streptomycin. Further studies were therefore undertaken in an attempt to determine whether the combination of isoniazid with pyrazinamide would demonstrate sufficient therapeutic superiority to justify its use, despite the hazard of hepatoxicity which had been shown to result from the use of pyrazinamide alone.

Patients selected for the treatment-study program had active cavitary pulmonary tuberculosis, had received no previous antituberculosis drugs, and tubercle bacilli were found in their sputum or in gastric cultures. They were assigned by random allocation to one of the following treatments: (1) isoniazid, 300 mg. daily, and para-aminosalicylic acid, 12 Gm. daily, or (2) isoniazid, 300 mg. daily and pyrazinamide, 3 Gm. daily. Previous reports have been made of preliminary observations and of this study, but it is now possible to give more complete analysis of the results.

Reports are available on at least 4 months of treatment of 237 patients given izoniazid and PAS and of 219 patients given izoniazid and pyrazinamide. It was observed that when pyrazinamide was given in a daily dosage of 3 Gm. it was equally as effective as, but not superior to, para-aminosalicylic acid as a companion drug for use with isoniazid. Hepatotoxicity was a significant hazard in the use of pyrazinamide. This drug, is, therefore, not recommended for use in the initial treatment of active pulmonary tuberculosis. It is recommended for use only in hospitals, where its toxicity is clearly understood, where the patient may be observed daily, and where regular liver function tests can be performed.

Reduction of Chronicity in Pulmonary Tuberculosis by Prednisone. P. K. Bornstein, K. G. S. Nair, and I. G. Epstein. Am. Rev. Resp. Dis. 81:421-422 (March) 1960 [New York].

About 20% of patients with active tuberculosis fail to respond to treatment with chemotherapeutic combinations. This failure is usually due to factors peculiar to the patient himself, such as low resistance or late detection. The tuberculosis process in these patients eventually becomes chronic and they become health hazards when they live outside institutions. The present study was initiated to determine the effectiveness of small doses of prednisone in a group of patients with potentially chronic tuberculosis. Fifty-two such patients were chosen and divided into 2 equal groups. The first group of patients served as controls, and the second group received prednisone. Patients selected had had a minimum of 4 months of antimicrobe therapy with no significant improvement. Sixteen of the treated patients were men and 10 were women. Roentgenograms taken before the treatment showed that 16 patients had far advanced and 10 had moderately advanced disease. The sputum of all these patients contained tubercle bacilli. Five patients had severe toxemia and were bedridden. All 26 patients were given 10 mg. of prednisone daily in 2 equally divided doses. Their antimicrobe drug therapy was not changed.

Approximately half of the 26 patients who were given prednisone showed significant improvement and were discharged from hospital with inactive disease. In the control group, only 2 patients had a similar outcome. No side-reactions were noted in spite of the prolonged therapy. These findings suggest that addition of prednisone be considered for patients who fail to improve with conventional antimicrobe therapy.

PATHOLOGY

Isolated Multiple Nodular Pulmonary Amyloidosis.

L. Weiss. Am. J. Clin. Path. 33:318-329 (April) 1960 [Baltimore].

The author reports autopsy findings in a 46-year-old man with isolated multiple nodular pulmonary amyloidosis, who had died 48 hours after his admission in stupor. There was a history of headache, fever and cough. Symptoms, signs, and laboratory data indicated a purulent meningitis. Previously obtained chest roentgenograms and physical findings had been suggestive of pulmonary tuberculosis.

Gross examination revealed obliteration of pleural cavities and interlobar fissures by tough fibrous adhesions. Numerous stony-hard, but deformable nodules were palpable in each lung. The lower lobe of the left lung contained a smooth, thick-walled, compressed cavity. The lower lobe of the right lung contained a well-defined unencapsulated, nonaerated, firm, elevated, dry, smooth, velvety, homogenous, pale yellow-pink area, 2 cm. in size, which lacked normal pulmonary architecture. The brain contained a recent abscess that had destroyed the right thalamus and adjacent tissue. Microscopic examination showed that the pulmonary nodules consisted of a homogeneous, eosinophilic material (amyloid) in broad masses, broken into fibrils and irregular masses, or deposited in a definite pattern. One pattern was a ring formation around a central capillary or a larger vessel. The scaffold of the alveolar walls might be followed, and extensions along alveolar walls and venules were frequent. Frequently a curious pattern resulted from a mixture of deposits in the alveolar walls and filling the alveoli. Secondary changes varied the appearance of the amyloid. Small ossifications frequently surrounding marrow-like foci, were noted. The bulk of the amyloid was almost acellular. Phagocytosed, intracellular, Congo red-positive amyloid, masses were observed in small groups of giant cells. The lesion in the right lung was composed of rather uniform, small, round cells, about 10 μ in diameter, arranged on a fine, delicate reticulum. These cells seemed to be lymphocytes; a few were suggestive of plasma cells. Several large, round, occasionally fused, intracellular inclusions were observed in a few scattered areas. Amyloid was not observed in the neoplasm, but only adjacent to it.

Pathological diagnoses of bilateral multiple nodular pulmonary amyloidosis, lymphoma, lung abscess, and brain abscess were made. Amyloidosis that is limited to pulmonary tissue, as in the case described, is an infrequent, but perhaps significant facet of the amyloid problem. The association with pulmonary lymphoma or plasmocytoma is apparently unique. The pathogenesis is discussed, in relation to the coexisting pulmonary plasmacytoid lymphoma and to secondary alterations, such as chondrification, calcification, ossification and giant cell reaction.

The Susceptibility of Staphylococci to Chloramphenicol. A Survey of Experimental and Clinical Experiences.

M. W. Fisher. A. M. A. Arch. Int. Med. 105:413-423 (March) 1960 [Chicago].

The author surveyed various experimental and clinical observations by American, British, Canadian, and French workers which revealed that there may be a unique relationship between chloramphenicol and staphylococci with respect to an infrequency of resistant strains. The following conclusions have been reached. The actual incidence of staphylococci which are truly resistant to chloramphenicol may be exaggerated by certain test methods and criteria. Experimentally, resistance to chloramphenicol develops slowly and only to a moderate degree. This suggests an intrinsic inability of staphylococci to acquire chloramphenicol resistance.

In man, chloramphenicol-resistant strains of staphylococci occur infrequently, and are of a moderate degree of resistance. In some instances they tend to back-mutate to a state of susceptibility, and they respond to increased dosages of this antibiotic in experimental infections. Contrary to the favored concept, the general incidence of chloramphenicol-resistant staphylococci does not appear to be related to the frequency or intensity of use of this antibiotic.

The principal aim of this survey was to obtain a better understanding of the available knowledge of the susceptibility of staphylococci to chloramphenicol. It is not implied that chloramphenicol-resistant strains of Staphylococcus aureus do not exist. This review does indicate, however, that when considering the choice of an antibiotic for the therapy of a staphylococcic infection, the problem of antibiotic resistance can be regarded as minimal for chloramphenicol.

The Sensitivity of Hemolytic Staphylococci to a Series of Antibiotics. II. A Three-Year Progress Report. R. G. Petersdorf, M. C. Rose, H. B. Minchew, and others. A. M. A. Arch. Int. Med. **105**:398-412 (March) 1960 [Chicago].

The authors tested the sensitivity of 300 strains of staphylococci, including 150 strains isolated from patients with clinical infections, 50 from carriers with recent infections, and 100 from asymptomatic carriers, to penicillin, erythromycin, chloramphenicol, tetracycline, neomycin, bacitracin, oleandomycin, triacetyloleandomycin (Signemycin), novobiocin, kanamycin, vancomycin, and ristocetin. A tube-dilution technique with determinations of bacteriostatic and bactericidal endpoints was employed. Although many strains were resistant to penicillin, nearly 50% were sensitive to a concentration of 50 units of penicillin per milliliter. Among the newer antibiotics vancomycin and kanamycin were potent bactericidal agents, while novobiocin, oleandomycin, and ristocetin inhibited but did not kill most strains. There has been no increase in resistance to chloramphenicol and erythromycin during the past 3 years, i. e., since 1957, when 1 of the authors published a report on tube-dilution sensitivity tests evaluating the activity of 10 antibiotics against 200 strains of hermolytic staphylococci.

Organisms lysed by bacteriophage 81 were uniformly resistant to high concentrations of penicillin and to tetracycline; these strains also tended to be slightly more resistant to most other agents. In general, tube-dilution sensitivities were in agreement with routine disks. Severe, systemic staphylococci infections acquired outside the hospital or caused by bacteriophage types other than 81 should be treated with large doses of penicillin, 20 million to 40 million units per day in conjunction with probenecid, and a 2nd agent such as chloramphenicol or erythromycin may be added to the regimen. In contrast, patients who have clearly acquired the infection in hospital, or whose causative Staphylococcus is lysed by bacteriophage 81, should be treated with vancomycin and chloramphenicol from the outset. Depending on the results of detailed in vitro tests, erythromycin, novobiocin, or oleandomycin may be substituted for chloramphenicol, and kanamycin, bacitracin, and neomycin (in order of preference) substituted for vancomycin. This program for the treatment of staphylococcic disease emphasizes that hospital-acquired infections should be treated with agents different from those used in infections acquired outside a hospital.

Hemochromatosis and Hemosiderosis: Study of 211 Autopsied Cases. R. A. MacDonald and G. K. Mallory. A. M. A. Arch. Int. Med. **105**:686-700 (May) 1960 [Chicago].

Among the records of 211 cases of hemochromatosis and hemosiderosis there were 57 cases of hemochromatosis, 104 of simple hemosiderosis, and 50 of advanced hemosiderosis. The chief complaints on admission to the hospital were nonhepatic neoplasm, pneumonia, heart failure, infection, and cerebrovascular disease. The most frequent causes of death were infectious disease and heart failures. The incidence of heart disease and death from heart failure was comparable to the incidence in other groups of the same age as in this series. Eighty-five per cent of the patients with hemochromatosis had a record of alcoholism. Three-fourths of the nonalcoholic patients had reported an inadequate diet or had fatty liver at autopsy. Eighty-three per cent of those with simple hemosiderosis and 57% of those with advanced hemosiderosis admitted to drinking excessively.

The authors believe that hemochromatosis and hemosiderosis are variants of a single disease, and that the abnormal absorption of iron may be caused by dietary, rather than by genetic, factors. There may also be a combination of factors, such as anemia or hematologic disease, causing excessive iron absorption, with transfusions or oral administration of iron contributing to the amount deposited in the tissues.

Liver Dehydrogenase Activity in Chronic Alcoholism: A Comparative Histochemical Study. S. W. French. A. M. A. Arch. Path. **69**:303-313 (March 1960 [Chicago].

Liver tissue was obtained from 25 alcoholics and 24 nonalcoholics by laparotomy, needle biopsy, or at autopsy. Tissue slices were prepared for histochemical assay of diphosphopyridine necleotide dehydrogenase (DPNHD) and succinic dehydrogenase system (SHD). The stages of liver damage in alcoholics were divided into 3 main categories: fatty liver, active cirrhosis, and inactive cirrhosis.

Necrotic liver cells associated with passive congestion or viral hepatitis showed no SHD or DPNHD activity, while liver cells containing bile plugs, lipofuchsin, and fat in nonalcoholics showed no reduction in SHD or DPNHD activity. Most fatty livers of alcoholic patients contained foci of liver cells which showed no DPNHD activity. These foci differed from the necrotic liver of nonalcoholics in 2 ways. (1) There was usually focal loss of

DPNHD activity, without loss of SHD in the fatty livers of alcoholics, while in nonalcoholics both SHD and DPNHD activities were absent in foci of liver necrosis. (2) Liver cell retaining DPNHD activity in fatty livers of alcoholics were found among groups of cells deprived of DPNHD activity, while DPNHD was uniformly lost in foci of liver necrosis in the nonalcoholics. Active cirrhosis in alcoholic patients was associated with focal liver-cell loss of both SHD and DPNHD activity. These differences suggest that the mechanism of focal enzyme inactivity in livers of alcoholic patients differs from that in central necrosis associated with passive congestion.

Persistence of enzyme activity in islands of cells containing no fat, in livers showing both cirrhosis and nodules of fatty degeneration, suggests that local differences to some extent determine loss of enzyme activity and the development of degenerative changes. Observations by several investigators indicate that blood bypasses lobular and nodular parenchyma in cirrhosis, and that dietary imbalance common in alcoholics leads to the development of fatty liver, reducing the activity of certain enzymes. Since SHD and DPNHD are derived from riboflavin, a relative riboflavin deficiency may participate in the development of liver-cell degenerative changes and in the reduction in SHD and DPNHD. Thus, ischemia and malnutrition may play a role in the pathogenesis of enzyme changes.

A Clinical and Autopsy Study of Tumor Cells in the Thoracic Duct Lymph. A. L. Watne, I. Hatiboglu, and G. E. Moore. Surg. Gynec. & Obst. 110:339-345 (March) 1960 [Chicago].

The authors performed cannulations of the thoracic duct in 30 patients with far-advanced carcinomas and sarcomas at the Roswell Park Memorial Institute in Buffalo. The thoracic duct was isolated according to Bierman's technique. To facilitate identification of the duct structure and the abdominal origin of the lymph, the patients were given a glass of milk 30 minutes before the surgical intervention, which produces a white lymph due to the increase in chylomicrons. The duct was incised transversely, and the flow of white chyle confirmed the gastrointestinal source of the lymph. A polyethylene catheter was inserted; it was tied in place with a no. 000 black silk suture. The wound was closed when it was ascertained that no leakage of lymph was present. Continuous drainage was maintained for as long as 12 days. The lymph was collected daily according to the technique of Linder and Blomstrand. Tumor cells were present in the lymph of the thoracic duct of 7 (23%) of the 30 patients. Of these 7 patients, 3 had carcinoma of the stomach, 2 had carcinoma of the lung, 1 had carcinoma of the breast, and 1 had carcinoma of the ovary. During the period of lymph flow there was some slight decrease in the serum albumin and globulin levels, but no decrease occurred in the serum cholesterol levels.

Postmortem studies were carried out on 600 patients. Due to the technical difficulty in obtaining lymph from the cisterna chyli, adequate examination was possible in only 91 patients, all of whom had died of widespread malignant disease. Tumor cells were present in the lymph of 15 of the 91 patients, or 16%. Tumor cells were present in the lymph of 3 (23%) of 13 patients with cancer of the breast, and in 3 (21%) of 14 patients with cancer of the lung.

It appeared from these clinical and autopsy findings that patients with carcinoma of the stomach, lung, and breast have a high incidence of tumor cells in the lymph. There was a positive correlation between supraclavicular node metastasis and tumor cells in the lymph; however, no correlation was found between pulmonary metastasis and tumor emboli in the lymph. Nevertheless, the authors believe that the passage of tumor cell emboli by way of the thoracic duct into the circulating blood is an important mode of cancer dissemination.

Cerebral Vascular Lesions and Peptic Ulceration. J. B. Dalgaard. A. M. A. Arch. Path. 69:359-370 (April) 1960 [Chicago].

Among 4,317 autopsies performed at the University Institutes of Pathology of Aarhus and Copenhagen, Denmark, and Bergen, Norway, 208 cases of acute and 177 cases of chronic peptic ulcers were observed. Of the 208 patients with acute peptic ulcers, including esophageal and gastric malacias, 67 (32%) had cerebral vascular lesions, and 33 (18.6%) of the 177 patients with chronic ulcers had such lesions. In 100 autopsies (2.3% of the total of 4,317) both cerebrovascular lesions and esophageal, gastric, or duodenal ulcers were found. Except for 3 patients with concomitant chronic ulcers, the patients with acute ulcers had no previous history of ulcer. They died after massive cerebral apoplexy, which obviously antedated, and without doubt caused, the acute ulcers incidentally found at autopsy. Most of these patients were unconscious previous to death and showed other severe primary symptoms, a fact which explains why the acute ulcers were not diagnosed in any of these patients. The interval from the onset of the apoplexy to death, with the ulcer established or malacia initiated, was less than 12 hours in isolated cases, and in most cases the interval was only a few days. This is consistent with known facts concerning the rapidity with which acute neurogenic ulcers may occur. No predominant sites of the lesions in the brain, notably no predominance of diencephalic lesions, could be found in these patients. Cerebrovascular lesions should be considered as frequent and clinically important causes of neurogenic peptic ulcers.

Experimental Staphylococcal Endocarditis in Dogs. II. Penicillin-Sensitive Mutants Arising from Penicillin-Resistant Staphylococcus Aureus During the Course of Experimental Canine Endocarditis. M. Hamburger, J. Carleton, W. F. Walder, and K. L. Clark. A. M. A. Arch. Int. Med. **105:**668-674 (May) 1960 [Chicago].

Aortic insufficiency was produced in 27 dogs by perforating an aortic cusp. Three weeks later each animal was given an intravenous inoculation of 10^6 to 10^7 staphylococci, a strain originally recovered from a human patient with acute endocarditis. Histological sections obtained at autopsy showed great masses of staphylococci imbedded in fibrin and often associated with polymorphonuclear infiltration of varying degrees. Penicillin-sensitive variants were recovered from the blood and tissues of 2 dogs, of which 1 was being treated with tetracycline when the penicillin-sensitive mutant appeared. The fact that the staphylococci had become resistant to tetracycline suggests a possible relationship between these 2 changes in antibiotic sensitivity. Two other dogs, infected with a more resistant Staphylococcus organism also yielded sensitive mutants at autopsy. Colonies recovered from the blood and tissues of 18 dogs inoculated with the penicillin-sensitive mutant retained their sensitivity after passage through penicillin-free broth, and also after storage. The sensitive mutants produced small amounts of penicillase. This fact and the increase in minimal inhibiting concentration after a week's penicillin treatment of the patient from whom the strains were derived raise the question of whether resistance might appear again in the sensitive mutants.

Variation in the Duration of Survival of Patients with the Chronic Leukemias. M. Feinleib and B. MacMahon. Blood **15:**332-349 (March) 1960 [New York].

The authors studied hospital records and obtained data on 649 patients in whom Leukemia had first been diagnosed between 1943 and 1952. Diagnosis had been based on marrow biopsy or on autopsy in 65% of the patients. Follow-up was complete to 1958 in 584 (90%) of the patients. Duration of survival was computed from the date of diagnosis. The life-table method and the method of maximum likelihood applied to the 3-parameter log-normal distribution were used to analyze the survival trends. Observations of other investigators on the logarithms of survival times are discussed, and it is pointed out that a method of estimating parameters, the details of the required calculations, and the nature of the mathematical assumptions involved were reported in an earlier paper.

The median duration of survival after diagnosis for the total sample was 11.65 months. Sixteen per cent of the patients survived longer than 43 months after diagnosis, and 9% survived for 5 years. The mean duration of symptoms prior to diagnosis was 5.1 months. Median durations were somewhat longer for women than for men and for patients with chronic lymphocytic leukemia than for those with chronic myelocytic leukemia. However, neither of these differences was statistically significant. The duration of survival after diagnosis was significantly shorter for patients with chronic myelocytic leukemia who were over 60 years of age than for any other age or diagnosis group. For patients with chronic lymphocytic leukemia, duration of survival was independent of age. Duration of survival after diagnosis was independent of the duration of symptoms prior to diagnosis. The median duration of survival for a group of patients in whom the diagnosis was made during examination for symptoms referable to some other condition was similar to that of those presenting with symptoms clearly referable to leukemia.

Jewish women with chronic lymphocytic leukemia showed a median duration of survival of 21.1 months, compared with 6.4 months for the non-Jewish women. Women with type B or AB blood with chronic myelocytic leukemia had median survivals of about 24 months after diagnosis, compared with about 10 months in those with type A or O blood.

Senile Cardiac Amyloidosis. L. Buerger and H. Braunstein. Am. J. Med. **28:**357-367 (March) 1960 [New York].

At the Cincinnati General Hospital, a number of cases of amyloidosis were encountered at autopsy between 1953 and 1957. Occurrence of amyloidosis in older persons and predominant deposits in the heart led to investigation into the incidence of senile cardiac amyloidosis. Two 4-year periods were selected for comparative study: (1) 1941 to 1944; (2) 1953 to 1956. Sections of heart stored from postmortem examinations performed during the 2 periods were re-examined. Sections with hyaline deposits that could conceivably represent amyloid were critically evaluated. In the age groups selected for study 986 autopsies were performed during period 1; in period 2, there were 1,325 examinations. Forty-two instances of senile cardiac amyloidosis were detected.

Amyloid was deposited interstitially in the myocardium, beneath the epicardium and endocardium, and in the heart valves. When it had accumulated in substantial amounts a peculiar rigidity was imparted to the tissue, and the classic waxy or lardaceous appearance was manifest. Classification of the study material by life decades revealed an increasing incidence of cardiac amyloidosis with age. A comparison of the relative incidence in the two 4-year periods showed a similar percentile incidence in all decennial cohorts but the 10th. In this cohort there were no examples of amyloidosis in 10 autopsies during period 1, whereas 8 examples appeared in 33 autopsies during period 2. This rise in incidence in the oldest age group resulted in an increase in over-all incidence from 1.22 to 2.26% in the reviewed periods.

The study revealed neither characteristic symptoms nor specific diagnostic methods by means of which a definite clinical diagnosis may be established. Cardiac failure may occur when amyloid is deposited in large quantities. The high incidence of this disease in older persons should suggest the diagnosis in all elderly patients with cardiac failure not explainable on the basis of other lesions.

Exfoliative Cytology Studies of Gastric Lavage.

D. L. Moyer and L. J. Zeldis. Am. J. Gastroenterol. 33:285-293 (March) 1960 [New York].

The authors made cytological studies of 105 specimens obtained by gastric lavage from 78 patients with major gastrointestinal symptoms. Sixty-four (86%) of the 78 patients had roentgenographic evidence of an upper gastrointestinal lesion. In 3 patients a clinical and roentgenographic diagnosis of carcinoma was made before cell studies were performed; others showed roentgenographic evidence of rugal folds, gastritis, or abdominal menses. Cells suggestive of, or consistent with, malignancy were identified in the gastric lavage specimens of 15 of 18 patients in whom a histological diagnosis of malignancy of the esophagus or stomach was subsequently made. In the remaining 3 of the 18 patients, the gastric lavage specimens yielded false negative cytological findings. These were found to be associated with 1 unusually large malignant ulcer and with 2 scirrhous carcinomas showing roentgenographic deformities characteristic of linitis plastica. There were false positive cytological findings (cells suggestive of malignancy) in the gastric lavage specimens obtained from 2 of 60 patients in whom the final pathological or clinical diagnosis was of a benign lesion. These false positive findings were associated with regenerating gastric mucosa in the margins of benign ulcers.

Exfoliative cytology is a useful adjunct to clinical and roentgenographic study of patients with major upper gastrointestinal symptoms and clinical findings suggestive of possible malignancy. Further evaluation of the procedure in patients with less well-defined clinical abnormalities is needed to determine whether it may contribute to earlier diagnosis of gastric carcinoma.

The Postmortem External Appearance of Congenitally Malformed Hearts as an Aid to Surgical Diagnosis.

A. H. Wilkinson Jr., W. J. Potts, and M. Lev. J. Thoracic & Cardiovas. Surg. 39:363-379 (March) 1960 [St. Louis].

The autopsy material which provided the basis for this study was taken from the Pathology Department at The Children's Memorial Hospital and from the Congenital Heart Disease Research and Training Center of the Hektoen Institute, Chicago. Two hundred ninety-six hearts were selected for evaluation. Many additional hearts were reviewed, but because of shapes distorted by fixation and previous study, they were not used in this work. Only children's hearts were studied. The aim of this study was to determine whether certain external anatomic features can be related to specific defects. Twenty-two complexes of congenital cardiac disease were studied. These are tabulated together with the number of cases in which each anomaly was observed. Several entities contained in the over-all classification were not considered in this study, either because sufficient material was not available or because the condition was one which was not, at the time, a diagnostic problem to the cardiac surgeon in the operating room. Five external features evaluated in each heart were (1) the over-all shape or outline of the heart as seen anteriorly, (2) the position of the anterior descending coronary artery and its relationship to the formation of the apex of the heart, (3) the size and position of the arterial trunk at the base, (4) the shape of the right basal border of the right ventricle, and (5) the visibility of the left atrial appendage as seen anteriorly.

It was found that the external morphology of the heart is a great aid in diagnosis in tetralogy of Fallot, tricuspid atresia, truncus *communis*, fetal coarctation, hypoplasia of the aortic tract complex, and total anomalous pulmonary venous drainage. It was also evident that the position and size of the arterial trunks and the course of the anterior descending coronary artery may be an aid to the diagnosis of a complex. While some subtypes of complete transposition can be differentiated with the aid of external topography, it is not possible to differentiate absolutely from the external topography alone the various types of septal defects. In an addendum the authors state that since this paper was written they have analyzed more than 50 additional congenitally malformed hearts. These have revealed 2 changes from the above observations. In 1 case of total anomalous pulmonary venous drainage into the coronary sinus, the anterior descending coronary artery was still seen anteriorly as in fetal coarctation. In several cases of partial transposition with pulmonary stenosis the shape of the heart resembled that of tetralogy of Fallot.

Studies on the Relationship of Staphylococcus Aureus to Pseudomembranous Enteritis and to Postantibiotic Enteritis.

W. H. Dearing, A. H. Baggenstoss, and L. A. Weed. Gastroenterology 38: 441-451 (March) 1960 [Baltimore].

These studies, carried out at the Mayo Clinic, aimed to determine whether all patients with postmortem-proved pseudomembranous enteritis or enterocolitis have culturable Staphylococcus aureus in the intestines and whether patients with severe postantibiotic staphylococcic enteritis have demonstrable lesions in the intestines. The authors present observations on 4 groups of patients: (1) eleven patients who died of extensive pseudomembranous enteritis or enterocolitis and in whom postmortem cultures revealed no Staphylococcus aureus; (2) eight patients who died of pseudomembranous enteritis or enterocolitis in whom postmortem intestinal cultures revealed Staphylococcus aureus organisms; (3) six patients with pseudomembranous enteritis or enterocolitis in whom no postmortem cultures were made; (4) patients with clinically and bacteriologically proved staphylococcic enteritis in whom no intestinal lesions were found at autopsy.

The authors found that fatal pseudomembranous enteritis or enterocolitis may have occurred in those patients in whom postmortem intestinal cultures failed to reveal Staphylococcus aureus, as well as in patients in whom such cultures revealed large numbers of such organisms. Severe staphylococcic enteritis may occur in patients in whom postmortem intestinal cultures reveal numerous Staphylococcus aureus organisms but in whom intestinal pseudomembranous lesions are absent. There is, however, evidence that these patients generally die of causes other than staphylococcic enteritis.

In Rochester (Mayo Clinic) hospitals, staphylococcic enteritis has been a relatively common disease which responded readily to antibiotic management, whereas pseudomembranous enteritis has been a rare disease which did not respond promptly to any known method of treatment.

Pseudomembranous enteritis is usually a fatal disease, whether Staphylococcus aureus is present in the intestine or not; the removal of Staphylococcus aureus from the intestine is not accompanied by reversal of the clinical picture, as is the case with simple staphylococcic enteritis. The reported studies are in accord with the concept that strains of Staphylococcus aureus resistant to penicillin, streptomycin, and the tetracycline derivatives constitute the etiologic agents in postantibiotic staphylococcic enteritis, but the fact that cases of pseudomembranous enteritis may occur without any culturable Staphylococcus aureus in the intestine casts doubt on the concept that all cases of pseudomembranous enteritis are produced by Staphylococcus aureus in the intestine.

Generalized Shwartzman-Like Reaction Following Serratia Marcescens Septicemia in a Fatal Burn.

C. D. Graber, W. T. Tumbusch, R. P. Rudnicki, and E. H. Vogel Jr. Surg. Gynec. & Obst. 110:443-450 (April) 1960 [Chicago].

The authors report the clinical course, postmortem findings, and immunological aspects of a 43-year-old soldier who sustained a 90% total body surface burn, 65% being full-thickness skin destruction, in a butane gas explosion. The severe burns were followed by Serratia marcescens septicemia and a generalized Shwartzman reaction. The patient died on the 5th postburn day in the Brooke Army Hospital in Fort Sam Houston, Texas, to which he had been evacuated on the day of burn. It is postulated that a combination of stress produced by severe trauma followed by an endotoxemia due to Serratia marcescens in the wounds, in the genitourinary tract, and in the blood stream caused the generalized Shwartzman reaction. In support of this concept, bacteriological and immunological work was performed on rabbits which showed that preparatory intradermal sensitization by the patient's Serratia marcescens endotoxin followed by an evoking intravenous injection of a dose of burned rat diffusate or human immune globulin could cause a local reaction. In view of these findings, it is suggested that Serratia marcescens, a chromogenic bacillus more commonly observed as a pyrogen in intravenously administered solutions than as a pathogen, should be seriously regarded as a potential bacteremic agent in burn trauma. The wisdom of using it as a tracer organism in human studies is challenged.

A Pathologic Study in 55 Autopsies After Radical Surgery for Cancer of the Cervix.

J. W. M. Kelly, L. Parsons, G. H. Friedell, and S. C. Sommers. Surg. Gynec. & Obst. 110:423-432 (April) 1960 [Chicago].

The authors report significant autopsy findings in 55 patients who had been subjected to surgical management for carcinoma of the cervix; hysterectomy alone was performed in 3, and it was associated with pelvic lymphadenectomy in 15, anterior pelvic exenteration in 7, and total pelvic exenteration in 30. The age of the patients ranged from 28 to 72 years, with approximately three fourths of them between the ages of 40 and 60 years. The preoperative clinical assessment of the extent of the disease was made more difficult in some cases by the reaction to previous irradiation therapy, but, even without this factor, pathological study of the surgical specimen showed that such assessment was frequently inaccurate. Lymphatic invasion at the primary tumor site was noted in slightly more than one-half of the cases, and blood vessel invasion in slightly less than one-half. The presence of positive lymph nodes in the surgical specimen was the most important prognostic feature regarding the presence of residual tumor at autopsy. Positive lymph nodes in the operative specimen appeared to indicate dissemination of tumor by other routes as well as by lymphatics to regional nodes. With an increasing volume of tumor at the primary site, positive lymph nodes were of increasing importance in indicating the probable presence of metastatic cancer at autopsy.

Urinary tract complications, both preoperative and postoperative, provided the most frequent problems in the clinical management of these patients, and they were partially or wholly responsible for a majority of the postoperative deaths. Such complications should be much less frequent in the future as surgical techniques improve, especially in anterior or total exenteration cases. Urinary tract complications due to recurrent tumor will undoubtedly continue to be seen in later stages of the disease.

The Pathologic Effects of Smoking Tobacco on the Trachea and Bronchial Mucosa. K. P. Knudtson. Am. J. Clin. Path. 33:310-317 (April) 1960 [Baltimore].

The author studied 150 lungs which were removed from men, aged 23 to 85 years, who had died at the Veterans Administration Hospital in Seattle, Washington, and on whom autopsies had been performed. A printed questionnaire was mailed to the next of kin of these men in order to obtain definitive data on the smoking history of the patients, their occupation, and place of residence. For microscopic examination, longitudinal strips of mucosa were removed, starting at the proximal cut margin of the trachea, and extending continuously to the periphery of the lower lobe of each lung. The strips were then coiled in a "Swiss role". Three to 5 sections were cut from each "Swiss role" and stained with hematoxylin and eosin. The changes noted were correlated with the history of smoking, age of the patient, occupation, and site of residence. Normal mucous membrane was observed in 50% of the specimens obtained from nonsmokers, as compared to that in 20% of the specimens obtained from heavy smokers. The carina was the most frequent site of metaplasia. Age, occupation, and the site of residence had no appreciable relation to the changes in the bronchial mucosa.

The author visualizes the sequence of changes in the mucosa of the respiratory tract as follows: basal cell hyperplasia with reduction in mucous secretion, followed by metaplasia of the basal elements to squamous epithelial cells, and maturation of these cells to form keratinized epithelium. The function of the cilia is thus lost, and normal secretions are further suppressed. Focal areas of epithelium are occasionally subjected to irritation and superimposed infections that result in atypical proliferative change. There is the impression that basal cell hyperplasia, squamous metaplasia, and atypical proliferative change represent changes significantly increasing in that order, and are in all probability consecutive states in mucosal transformation to cancer of the lung.

Isolated Vestiges of Calcified Syncytial Knots ("Orphan Bodies") in the Stroma of Chorionic Villi: Their Genesis and Implication. Y. Ishizaki. Obst. & Gynec. 15:528-534 (April) 1960 [New York].

The author reports on the morphology, genesis, and implication of vestiges of calcified syncytial knots, isolated in the stroma of chorionic villi without any connection with the trophoblastic layers covering the villi. These structures are vestiges of calcified syncytial knots which later became involved in foci of placentitis. Although the original villi were destroyed by the inflammation, the syncytial knots, having been calcified, survived the affects of the inflammation; with the completion of the organization of the foci, they became buried in the newly formed villi. The term "orphan bodies" was given to the isolated vestiges of calcified syncytial knots in the stroma of villi. They thus mark sites of healed placentitis. "Orphan bodies" were found in 115 of 270 placentas from mothers consecutively delivered. In most instances, only few "orphan bodies" were found in whole sections, while in some, numerous "orphan bodies" were seen in each section. The majority of "orphan bodies" contain some iron in addition to calcium. Both iron and calcium increase in quantity according to the length of duration of the lesions. The possibility is suggested that healing of placentitis may result in formation of anastomoses among the chorionic villi "glued" together by the exudates in the foci.

Role of the Halo Cell in Cervical Cancerigenesis: A Virus Manifestation in Premalignancy? J. E. Ayre. Obst. & Gynec. 15:481-491 (April) 1960 [New York].

Cytological studies on scrapings from cervical lesions from 246 patients revealed halo cells in 47 of them. Of these patients, 33 were in the minimal precancer cell complex stage and 11 were in the borderline inflammatory stage with precancerous tendencies. No patients showing normal cytological findings exhibited halo cells, and only 1 of 41 patients with cancer in situ showed halo cells. Thus it appears that halo cells are found exclusively at the borderline between chronic infectious or inflammatory activity and extremely early cell manifestations of premalignancy. It appears plausible that the cell may be in the process of being launched upon its course of accelerated replication, and that viral infection with a persistent estrogenic influence operates to cause the first mutant change to malignancy, creating cells with early abnormal growth characteristics, followed later by additional mutant changes as accelerated growth and invasion follow. Presumably some measure of fibrosis occurs in the subepithelial stroma in the region of the squamocolumnar junction, which diminishes the supply of blood and oxygen to epithelial cells in the junctional area. Hence, reduced oxygen may be a factor. If estrogenic influence is reflected in cornification (estrogen may become concentrated in the chronically inflamed tissues of the cervix, possibly as part of a defense mechanism), then halo cells develop in an environment of continuous (acyclic) estrogenic activity. Estrogen in the cervical mucus probably plays a contributory role as it bathes cells in the region of the cervical os.

Human Tissue Preservation: Development of Regulations and Removal of Some Legal Barriers.

W. M. Chapman. California Med. 92:217-219 (March) 1960 [San Francisco].

Human tissue must be obtained promptly after death if it is to be successfully preserved. Legal assistance toward this goal has been established by the California Legislature. To implement this legislation the State Board of Public Health has established regulations relating to human tissue preservation. These are the first such regulations in the nation. Tissue preservation is not yet fully developed. Much research is in progress to overcome many problems. It is believed that the California laws and regulations will remove legal obstacles and lubricate the administrative machinery for the bequesting of tissues by persons before they die, thus allowing opportunity to use these tissues therapeutically and scientfically at the earliest possible moment. These regulations will also be an encouragement to new centers of tissue preservation both for therapeutic use and for the advancement of the horizons of knowledge so that when greater use of human tissue is scientifically possible the legal and administrative tools will be available with which to promote development in this field.

RADIOLOGY

Roentgen Therapy of Skin and Lip Carcinoma: Factors Influencing Success and Failure.

C. F. von Essen. Am. J. Roentgenol. 83:556-570 (March) 1960 [Springfield, Ill.].

The records of 1,100 patients with a total of 1,355 epitheliomas of the skin and mucosa of the lip were studied. Over 50% of the lesions were treated by roentgen therapy. A smaller number were excised or treated by radium. Five hundred sixty-five tumors treated by roentgen therapy satisfied all of the criteria enumerated below and form the basis of the present analysis. These criteria were (1) biopsy and microscopic diagnosis of invasive epithelioma (several smaller lesions were excluded because the biopsy, as determined by study of the microscopic sections, may have removed the entire epithelioma; lesions without biopsy were included only in the few cases where a proved recurrence or overdosage reaction developed); (2) treatment by roentgen therapy; (3) a minimum of 3 years of follow-up examination. Two hundred ninety-two lesions (52%) were followed for at least 5 years; 49 lesions (8.7%) were followed and observed for at least 10 years. It was found that 38 of the 45 recurrences developed within the first 3 years following treatment but that only 14 of the 29 necroses appeared in this period. The apparent peak for development of skin necrosis was in the 4th year following treatment, while the peak for recurrence was in the 1st year. It appeared that the adequacy of this minimum follow-up period was more limited in detecting overdosage reactions than in detecting recurrent neoplasms.

The author points out that in addition to dosage, the factors appearing to influence treatment results are tumor size and previous unsuccessful treatment. The time-dosage relationship was studied with reference to these factors.

Leukemia in Hiroshima Atomic Bomb Survivors.

R. Heyssel, A. B. Brill, L. A. Woodbury, and others. Blood 15:313-331 (March) 1960 [New York].

The best estimate of the population of Hiroshima at the time of bombing suggests that of the 225,000 civilians living in the city 64,600 were killed and 72,200 were injured. Immediately after the bombing the surviving population was widely dispersed, but the 1950 Atomic Bomb Survivors Survey enumerated the exposed population at 90,000. Hiroshima is a commercial city which is growing continuously by virtue of a rapid influx of nonexposed persons. Since 1948, scientists of the Atomic Bomb Casualty Commission (ABCC) in cooperation with physicians in Hiroshima have made efforts to detect hematological and other abnormalities in both the exposed and unexposed segments of the population. By Dec. 31, 1957, the Atomic Bomb Casualty Commission had knowledge of 130 people exposed in Hiroshima who were said to have leukemia. An additional 19 were diagnosed as having aplastic anemia or a leukemia-related disease, exclusive of the lymphomas. For each of these diagnoses, confirmation was sought by review of blood and bone marrow smears and any other available material.

General aspects of leukemia are discussed, such as its rising incidence throughout the world, the possible relation of the acute radiation syndrome to leukemia, and types of leukemia. As regards the exposed survivors, the authors discuss the expected rate of development of leukemia, its natural history. and other diseases of myeloid type. The material presented confirms the leukemogenic property of radiation. The incidence of leukemia is higher among those closely exposed than among those more remote from the hypocenter. This increase was first manifest approximately 3 years after exposure. It apparently reached its peak between 1950 and 1952. Since then, the incidence has been diminishing, but 13 years after exposure it is still higher than would be expected in the general population. The type of leukemia most increased in incidence is the chronic granulocytic variety. No apparent difference in the natural history of the specific types of leukemia in exposed and nonexposed Japanese has been observed. Preliminary analysis of the data shows a linear relation between a dose of radiation above 50 to 100 r and the incidence of leukemia. Below this dose, the shape of the curve is not certain.

Werner's Syndrome: A Clinical-Roentgen Entity. H. G. Jacobson, G. Rifkin, and D. Sucker-Franklin. Radiology 74:373-385 (March) 1960 [Syracuse, N. Y.].

The author reviewed the records of 8 patients with Werner's syndrome seen at the Montefiore Hospital, New York City, since 1930. Age at onset of 1st symptoms varied from 15 to 37 years. All patients were of Jewish descent. The following signs or symptoms were observed in all patients: eye abnormalities (cataracts); abnormalities of hair growth with early graying; taut, shiny and scleroderma-like skin; positive familial history; and ulcerations of the lower extremities, particularly about the bony points (malleoli). Cardiac abnormalities were observed in 8 patients, diabetes in 8, voice abnormalities in 6, abnormally small genitalia or a history of functional hypogonadism in 7, and presence of malignant tumors in 3. At least 3 patients died of a myocardial infarct.

The significant roentgenographic findings included osteoporosis, small bone stature, soft-tissue atrophy of the extremities, peripheral arterial calcification, metastatic calcification of soft tissues, neurotrophic changes in the bones of the feet, gross foot deformities, osteomyelitic or osteomyelitic-like lesions of the extremities, or both, osteoarthritis of the peripheral joints and spondylosis deformans. There were also abnormal cardiac findings, including heart enlargement, valve calcifications, and coronary artery calcifications.

Radiation: Registration of Sources. D. F. Dullum. California Med. 92:198-200 (March) 1960 [San Francisco].

Registration of sources of ionizing radiation, including x-ray machines and radioactive material used in the healing professions, is required by legislation recently enacted in California. Registration will provide information concerning the type and location of sources of radiation and will provide a basis for the evaluation of a need for additional radiation control and protection measures in the future. As the medical uses of radiation procedures constitute a major portion of the total radiation exposure of the entire population, it becomes increasingly important that physicians should develop a reasonable and knowledgeable concept not only of the obvious benefits but also of the actual and potential hazards of radiation as used in medicine. Practical and effective measures to minimize patient exposure, based on professional knowledge, competence, and experience, with profession-wide participation and support, will insure the effective integration of the medical uses of radiation in the California Atomic Energy Development and Radiation Protection Program.

ANESTHESIA

Physiologic Studies During High Flow, Normothermic, Whole Body Perfusion. D. C. McGoon, E. A. Moffitt, R. A. Theye, and J. W. Kirklin. J. Thoracic and Cardiovas. Surg. 39:275-287 (March) 1960 [St. Louis].

The authors discuss a system of high-flow normothermic perfusion which is used, and has been found clinically satisfactory, at the Mayo Clinic. The system utilizes a Gibbon-Mayo oxygenator and a steady rate of blood flow of approximately 2.3 liters per square meter of body surface per minute. Three patients requiring open-heart operation for repair of uncomplicated congenital heart lesions, were selected for physiological evaluation of this system of whole-body perfusion during operation. The 1st patient was a 10-year-old girl whose only symptom was easy fatigability and in whom cardiac catheterization had indicated the presence of both atrial and septal defects. She weighed 36 kg. (79 lb.), and her body surface was 1.24 sq. m. At operation an atrial septal defect was repaired, but ventriculotomy revealed an intact ventricular septum. Her recovery was uneventful. In the 2nd patient, a 9-year-old boy who weighed 41 kg. (90 lb.) and whose body surface was 1.24 sq. m., a typical high ventricular septal defect was identified at operation and was repaired by direct suture. The 3rd patient, a 9-year-old boy who weighed only 23 kg. (51 lb.), had a body surface area of 0.94 sq. m. He had a large patent ductus which was doubly ligated at operation.

Mean arterial blood pressure became subnormal at the start of perfusion but tended to return progressively toward normal as the result of an increasing peripheral vascular resistance. Venous pressure remained steady and at a satisfactory level. Large size of the venous and arterial cannulas permitted minimal pressure gradients across them. Metabolic acidosis of mild degree, compensated by respiratory alkalosis, occurred as a result of general anesthesia and manual hyperventilation, but perfusion caused no appreciably greater metabolic acidosis. Oxygen consumption during perfusion was found to be within normal limits for anesthetized man, and the oxygen saturation of venous-blood hemoglobin was only slightly subnormal. The blood was fully arterialized by passage through the oxygenator. The rate of blood flow employed during these perfusions is believed to be nearly as great as the rate of blood flow maintained by the functioning heart of the anesthetized patient.

Use of Halothane (Fluothane) in Obstetric Anesthesia: Preliminary Report. J. A. Cutter and B. D. King. New York J. Med. 60:503-511 (Feb. 15) 1960 [New York].

The authors report on 223 pregnant women with vaginal deliveries. Of these deliveries, 170 were accomplished with the aid of anesthesia produced by halothane (Fluothane), and 53 were performed with the aid of anesthesia produced by chloroform. The effects of these anesthetic agents on mothers and infants were studied. In comparison with chloroform, halothane was found to produce less uterine relaxation, a superior condition in the infant, a more rapid induction of and recovery from anesthesia, and fewer undesirable side-effects. Halothane was found to be 1½ times more potent than chloroform. Uterine relaxation, excessive bleeding, and profound blood pressure depression were not noted in this series, which is in contrast to reports by other workers who did observe these complications. The absence of such complications can be explained by the fact that light anesthesia and carefully controlled concentrations of halothane were employed. The agent was volatilized in a Fluotec vaporizer, which compensates for both temperature change and flow variations of 4 to 14 liters per minute. Gases used for the vaporization of halothane were nitrous oxide and oxygen. The maximum concentration of nitrous oxide employed was 75%. Total gas flows were constantly altered within the range of 8 to 20 liters in order to maintain a full reservoir bag.

It is often difficult for the anesthetist who administers halothane for the first time to appreciate the marked difference which can be produced by an alteration in concentration of a few tenths of 1%. Confirmation of this potency has convinced the authors of the validity of the following principles for safe administration of halothane: (1) vaporization in an accurately calibrated flow-and-temperature-compensated vaporizer, (2) utilization of a nonrebreathing system, and (3) administration by an anesthetist experienced in the properties of the agent.

Clinical Study of Chloroform Anesthesia: A Preliminary Report. J. G. Reynolds, D. M. Thomas, and E. H. Conner. J. Kentucky M. A. 58:340-344 (March) 1960 [Louisville, Ky.].

The authors report on 62 unselected patients, between the ages of 20 months and 88 years, to whom 65 trichloromethane (chloroform) was administered. The duration of anesthesia varied from 30 minutes to 10½ hours. Anesthesia was induced either with thiopental sodium or with a combination of chloroform nitrous oxide and oxygen. When intubation of the trachea was performed, succinylcholine chloride, in doses of 40 to 60 mg., was used to provide muscular relaxation. The concentration of chloroform was not allowed to exceed 2%, and, during maintenance, chloroform concentrations were held below 1%, usually ranging from 0.4 to 0.6%. Thymol turbidity and cephalin cholesterol flocculation tests of hepatic function were carried out in 31 of these patients. The tests showed no significant damage to the liver after chloroform anesthesia. Profound depression of the cardiovascular system with either sudden collapse or progressive fall in blood pressure during anesthesia was not observed in these patients, provided that the concentration of chloroform was under close control, that adequate ventilation was assured, and that hypoxia and hypercapnia were avoided. Controlled dosage, adequate ventilation, and careful observation of the patient at all times are important factors in insuring safe administration of chloroform.

PHYSIOLOGY

Diet-Type (Fats Constant) and Blood Lipids in Man. A. Keys, J. T. Anderson, and F. Grande. J. Nutrition 70:257-266 (Feb.) 1960 [Philadelphia].

It has been suggested that dietary characteristics other than fat content may contribute to the striking differences in serum cholesterol levels observed in comparisons between populations. The diets of populations with lower levels of blood lipids contain large quantities of fruits and vegetables. Such diets tend to be high in complex carbohydrates such as pectins, hemicelluloses and fiber, and in sugars other than sucrose. The authors report the results of comparisons between 2 kinds of diets differing in type of carbohydrate. One, which they have termed the "American type," is relatively low in fruits and fresh vegetables and high in sucrose as compared with the other, the "Italian type." Both low fat (AL and IL) and moderate fat (AM and IM) versions of each type were used.

Twenty-eight male schizophrenic patients from 41 to 63 years old and between 66 and 115% of average body weight for height and age were the subjects. They were normal in physical health and none had erratic eating habits. The patients were divided into 4 sub-groups of 7 men each, matched as to age, relative body weight, and degree of physical activity. Body weights were measured once a week before breakfast, and calorie intakes were adjusted. Total cholesterol in the fasting serum of each man was determined on 4 occasions during each of the two 6-week dietary periods.

Diets AL and IL provided 13% of calories from protein and 16% from fats and were identical, except that 17% of total calories from sucrose and milk carbohydrate in diet AL were exchanged in diet IL for an equal number of calories in carbohydrates in fresh fruits, vegetables, and legumes, and except for the small accompanying exchange of proteins involving 4% of calories. Seven men subsisted on diet AL and then changed to diet IL for 6 weeks each, while 7 matched men made the reverse change. Similarly, 2 matched groups of 7 men each subsisted in crossover experiments on diets IM and AM, which corresponded to diets IL and AL except that total fats provided 31% of calories. Serum cholesterol levels averaged 16 mg. per 100 ml. lower on the IL than on the AL diet and 19 mg. per 100 ml. lower on the IM than on the AM diet; these differences were statistically highly significant. Gas chromatograph analysis of the extracted mixed fats from the diets as fed indicated equality of IL versus AL and of IM versus AM diet in polyunsaturated fats, but the IL and IM diets provided slightly higher amounts of saturated fats than the AL and AM diets. These fat differences would, of themselves, produce slight serum cholesterol differences (about 3 mg. per 100 ml.) in the direction opposite to that observed. It is concluded that sucrose and milk sugar tend to produce higher serum cholesterol values than equal calories of carbohydrates contained in fruits, leafy vegetables, and legumes.

Stimulation of Granulation Tissue Growth by Tissue Extracts. Study in Intramuscular Wounds in Rabbits.

R. H. Edwards, S. S. Sarmenta, and G. M. Hass. A. M. A. Arch. Path. 69:286-302 (March) 1960 [Chicago].

The authors studied the growth and development of connective tissue by inserting a polyvinil sponge (Ivalon) into subcutaneous tissues of rabbits. This insertion served as a spatial defect, creating a condition similar to that in a closed wound. Tissue extracts were prepared from 8-day chick embryos, autologous rabbit spleen, or autologous granulation tissue removed from thigh muscles 5 days after crushing. These extracts were homogenized in Tyrode's solution and mixed in equal parts with heparinized plasma. A dry, experimental sponge was immersed in this mixture, the air bubbles were extracted by mechanical pressure, and within 1 or 2 minutes the mixture formed a solid clot throughout the sponge. A control sponge containing a mixture of equal parts of plasma and Tyrode's solution was prepared, to be used after a clot had formed throughout the interstices. Twenty rabbits were used for each kind of tissue extract. The experimental and the control sponges were inserted, at the same level, in the rabbits' paravertebral muscle, under local anesthesia. The animals were killed at intervals of from 2 days to 3 weeks. The sponges and surrounding tissues were fixed in formalin and cross sections were prepared for microscopic study.

A minor hemorrhage was observed around the sponges immediately after the implantation. Two days later there was marked fibroblastic proliferation directly adjacent to the sponges, and occasional fibroblasts were found invading the clot in the marginal peripheral interstices. The peripheral pores of the control sponges contained residual leukocytes, wandering macrophages, and fibrin, while in the sponges saturated with tissue extract the concentration of fibroblasts in the peripheral pores was consistently increased. There was an increased number of fibroblasts and a deeper penetration of all components of granulation tissue into the pores of the experimental sponges at all comparable time intervals. An inflammatory reaction was observed in the sponges saturated with autologous chick embryo plasma extract, probably due to the presence of foreign protein from the chick embryo or adherent components of the egg.

The authors believe that this study demonstrated the possibility of increasing the rate of fibroplastic proliferation, capillary formation, and maturation of newly formed collagen in granulation tissue growing into a closed plasma clot system within a wound, by addition of tissue extracts to the system.

BOOK REVIEWS

Cardiology: An Encyclopedia of the Cardiovascular System. Volume 1: Normal Heart and Vessels. Volume 2: Methods. Volume 3: Clinical Cardiology. Volume 4: Clinical Cardiology—Therapy. Sponsored by American College of Cardiology. Edited by Aldo A. Luisada, M.D. Foreword by Ashton Graybiel, M.D. Cloth. Loose-leaf $100. Various pagination, with illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E. C. 4, England; 253 Spadina Rd., Toronto 4, Canada, 1959.

The ideas and reasoning that have brought about the composition of this encyclopedia cannot be better stated than is done in the foreword and the preface of each volume. "The American College of Cardiology, dedicated to the continuing education of its membership, is simply fulfilling one of its obligations. This book contains authoritative information abstracted from an immense mass of medical literature which could not be reviewed effectively by an individual. . . . Admittedly a work of this sort represents a form of communication in which there is much redundancy. . . . A modern encyclopedia of cardiology ought to have the following characteristics: (1) It should encompass all available knowledge on the heart and vessels, including history, embryology, anatomy, physiology, physical and technical methods of examination, bacteriology and pathology, clinical sciences, surgery, pharmacology and therapy, rehabilitation, and the various 'allied fields.' (2) It should present them in a systematic order, thus permitting easy consultation. (3) It should be of loose-leaf type, in order to keep abreast of medical progress."

Volume 1 describes the anatomy and physiology of the circulatory system. Leading into the anatomic considerations are two brief sections: one is on cardiac and vessel embryology, and the other is on blood circulation in the fetus and changes affected at birth. There is also a short introduction to the anatomic description which emphasizes the importance of anatomy in relation to recent advances in cardiovascular surgery and individual body variations of the heart and vascular tree; there is also a description of the circulatory segmentation of the liver and the lung. The section on the physiological functions of the heart and circulatory system is commendably thorough. In the second volume, the detail on both general and specific techniques of examination of the whole patient in regard to cardiovascular diseases is indicated in the first two chapters. Before the subject of physical diagnosis is presented the physiological implications of the medical interview and the general principles of obtaining a clinical history are reviewed. The latter half of the volume deals with electrocardiography, vectorcardiography, circulation time, and studies of blood. The information is so written that it can be understood by medical students as well as physicians, who are more advanced in cardiology.

The practical aspects of heart diseases—cause, effect, treatment, and results—are set forth in volumes 3 and 4. For diseases the causes of which are not yet known such information as is pertinent to the subject is discussed in detail. Although there is much material to consider, the conclusions are short and concise. Management of a patient with heart failure, as presented here, varies little from that outlined in standard textbooks. The volumes are ended with a discussion of the prevention of heart disease and rehabilitation of the patient who has suffered cardiac damage. The complete coverage, size, and cost of this encyclopedia indicates its value to physicians. It deserves a place in the libraries of large medical clinics, hospitals, and medical schools. The style of writing is such that physicians, whether in active practice or research, should benefit from all four volumes.

THEODORE JOHNSON, M.D.

Ciba Foundation Colloquia on Ageing. Volume 5: The Lifespan of Animals. Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor, B.A. With cumulative index to volumes 1-5. Cloth. $9.50. Pp. 324, with 58 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W. 1, England, 1959.

This volume contains a miscellany of papers and the group discussions that followed them at the fifth Ciba Colloquium on Aging. Among the topics presented are the effect of parental age on the longevity of man and of racehorses; aging in bees, Drosophila, and other insects; aging in fish, both in nature and in captivity; the lifespan of and arteriosclerosis in birds; and the relation of the age of onset of degenerative disease to the lifespan of the rat and of man. It is, however, in the group discussions that the greatest interest lies. Through these discussions attention is drawn to the tremendous gaps in the knowledge of aging, which handicap man's attempts to postpone and ameliorate senescence. Important problems of the study of aging are those of time and cost; many experiments, to be conducted properly, need 30 to 100 years of research before conclusive data can be collected even in a single investigation.

In these discussions a criticism is made of much of the work with experimental tumors. There is a tendency for investigators to transplant tumors to young, vigorous, and often rapidly growing animals and to report the results of chemotherapeutic tests on such tumors. Since tumors are essentially a problem of degeneration and senescence, does the study of the chemotherapy of tumors unrelated to the aging process have application to the treatment of tumors occurring under natural conditions? Some other unanswered and thought-provoking questions are as follows: Would birds develop arteriosclerosis if they were less well fed and if they had to hustle for their food? Why have mammary tumors not been seen in cows; are they immune or are they slaughtered too early for such tumors to develop? While this book should prove interesting to the experimental gerontologist and to any biologist interested in the processes of aging, it is neither a systematic textbook nor a ready reference tool. If the reader simply wishes to know how long his pet is likely to live, this is not the book for him.

HELEN MARSHALL

Carter's Microbiology and Pathology. By Alice Lorraine Smith, A.B., M.D., Professor of Pathology, Graduate Research Institute of Baylor University, Dallas, Texas. Seventh edition. Cloth. $7.50. Pp. 742, with 316 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1960.

The author has followed Dr. Carter's methods of presentation, giving the new enlarged and improved edition the unique features of the previous volumes, but she has rearranged the old and added new material. The illustrations are refreshing, practical, and instructive and include photographs, tables, and charts that add visual interest and clarity to subjects that might be difficult to understand. The historical chapters on microbiology and pathology are excellent introductions to these subjects.

Sections on microbiology include modern classification, nomenclature, descriptions of bacteria and viruses, and pertinent immunological, public health, and clinical applications. The staphylococcus problem in hospitals is briefly discussed and deserves more amplification as its epidemic importance has grown. The subject of parasitology is included with good illustrations. Case histories of bacterial, fungal, and viral diseases are instructive features. Chapters on inhibition and destruction of microbes by various modern means are particularly valuable to hospital personnel. Allergic phenomena, skin testing, and applied immunology are briefly but well described and illustrated. In the section on pathology, the pathologist in an average hospital is depicted with particular reference to his role in clinical chemistry, microbiology, parasitology, serology, surgical pathology, and autopsies. The chapters on basic principles are brief and are supplemented by good descriptions of pathological processes in various systems. The etiological basis of disease processes is emphasized, and new data on the reaction to injury include important poisonous agents, isotopes, and the effects of atomic radiation. At the end of each chapter, pertinent questions are listed for review. A glossary of terms is another unique feature. This edition is a popular and worthy textbook for instruction of nurses; it can also be recommended to medical students and busy practitioners who want a practical quick reference to the essentials of microbiology and pathology.

ISADORE PILOT, M.D.

Glaucoma: Transactions of the Fourth Conference, March 8, 9, and 10, 1959, Princeton, N. J. Edited by Frank W. Newell, M.D. Sponsored by Josiah Macy, Jr. Foundation. Cloth. $8. Pp. 257, with 108 illustrations. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York 36, 1960.

The discussion of the Fourth Conference on Glaucoma is reported in the same way in which previous discussions have been recorded. There are brief, formal statements by the participants, frequently interrupted by questions and followed by free discussion. The remarks, both formal and informal, are reported just as they were made. The subjects of the conference were the fine structure of normal trabecular apparatus in man (A. S. Holmberg); the role of trabecular structure in the problem of simple glaucoma (Norman Ashton); ultrastructure of the ciliary epithelium and its relationship to aqueous secretion (A. S. Holmberg); and pathological findings on six eyes with primary glaucoma (A. L. Kornzweig).

The clinician will find neither the formal presentations nor the group discussions as interesting as those of the previous conferences, and he will be surprised that there should be so much disagreement on the interpretation of histological findings, both normal and pathological. The fact is that the histopathological changes of glaucoma remain unknown. From the reader's standpoint, there would be less confusion if each essayist had made a complete statement of his findings and his conclusions which could have been the subject of discussion. Also some sort of summarizing statement, even if only to define areas of disagreement on the part of the participants, would have added to the reader's understanding. Faced with the handicaps of reporting such a discussion, the editor has done a skillful job of organizing the material.

DANIEL SNYDACKER, M.D.

Music Therapy 1958. Volume VIII: Eighth Book of Proceedings of the National Association for Music Therapy, Inc., Founded 1950. Papers from ninth annual conference, Cincinnati, Ohio. Editor: Erwin H. Schneider, Ph.D. Associate editor: Ruth Boxberger. Cloth. $5.20. Pp. 331. Allen Press, Lawrence, Kan., 1959.

This book, the eighth in a series of annual volumes on music therapy, reminds one again that sound can be welcome or unwelcome, that unwelcome sound is noise, and that the increasing resources of the mechanized music industry have placed in human hands a two-edged weapon. In any large institution a surprising amount of money is likely to be invested in pianos, phonographs, radios, musical instruments, and auditoriums. Misused, such facilities can be worse than wasted. Properly used, they can not only give pleasure but can have extraordinary effects on the patient and on the atmosphere of the entire surroundings.

This volume consists of contributions by many authors. The chapters average about 10 pages in length and are grouped to deal with the views of hospital administrators, the show as a therapeutic instrument, group psychotherapy, music in physical medicine, music therapy and special education (as in mental hospitals), music therapy for exceptional children, dance therapy, volunteer services in music therapy, special applications to mentally ill, physically disabled or mentally retarded groups, and research in music therapy. The concluding pages are devoted to organizational news, a bibliography of music therapy including both recent and earlier publications, an appendix of organizational information, and an index.

Some space is wasted in this book by the repetition of vague platitudes, but in general the varied contributions have been woven into a well-integrated whole. Some of the contributions are outstanding for the quality of scientific work on which they are based, the understanding of human nature which they reveal, and the interesting detail with which some points are illustrated. At once lively and penetrating is a psychiatrist's description of a show given by the patients in a county hospital. This volume is a reassuring indication that music therapy is not only maturing as an art but is also strengthening its foundations as a science.

F. T. Jung, M.D.

Microchemical Methods for Blood Analysis. By Wendell T. Caraway, Ph.D., Biochemist, Flint Medical Laboratory, Flint, Michigan. Cloth. $5.25. Pp. 109, with 4 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

This book, clearly and in detail, describes the equipment and methods for the performance of many chemical analyses of the blood useful in the practice of clinical medicine. Microtechniques require from 0.02 to 0.1 ml. of serum, and thus capillary as well as venous blood may be used. The author addresses himself not to experienced chemists but to those beginning in the field or without wide experience and to those whose primary interests may not be in clinical chemistry but who may have some responsibility for laboratory procedures. Viewed in this perspective, the volume is valuable because it gives detailed information on matters that the experienced chemist would take for granted. For example, the names of supply houses for a particular item of equipment are listed. The author also tells how to wash and calibrate pipets and how to prepare, store, and test reagents.

Each method is preceded by a brief discussion of the chemistry involved. The steps for various procedures are outlined, the necessary calculations explained, and normal values indicated. All methods are derived from standard procedures in current use and are accompanied by the original and other references. The book does not critically discuss each method and gives only one method for the determination of a given chemical constituent. The author stresses the need for quality control of each day's analysis of a given substance. A standard pooled serum reagent of known composition should be run concurrently whenever an unknown sample is analyzed. The limitations of this volume spring largely from its fundamental objective of simplicity and straightforward presentation.

Wm. E. Connor, M.D.

Photography in Medicine. By Arthur Smialowski, Director, Department of Photography, St. Michael's Hospital, Toronto, Canada, and Donald J. Currie, M.D., M.Sc., F.R.C.S.E., Attending Staff Surgeon and Consultant to Department of Photography, St. Michael's Hospital. Cloth. $14.50. Pp. 330, with 314 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

This publication purports to be a handbook "on established techniques, new techniques, and new photographic arrangements." It is advertised as the "first comprehensive text to deal exclusively with the many applications of photography in the science and practice of medicine." Such a handbook should provide a long-needed source of authoritative information, but this publication falls short of being an authoritative compendium of the subject because of its superficiality in most of the areas which it endeavors to cover.

Too few pages are allotted to the explanation of scientific photographic specialities; this exacting speciality usually requires volumes for adequate working knowledge and description. For example, the chapter on photomicrography amounts to less than 17 pages of text (including 13 illustrations). Although an important aspect of photographic medical recording is the use of motion pictures, these authors skim through an introduction to the subject and describe the selection of equipment, sound recording, film selection, studio furniture, light sources, rehearsal, script writing, film editing, filming procedures, title selection, and film processing in 13½ pages including the illustrations.

The chapter entitled Photography by Invisible Radiation covers infrared, ultraviolet, and radioactive radiation in less than 11 pages. This book will disappoint the seriously inclined seeker of knowledge who is conditioned by handbook acclimatization in other fields. If it can be considered as an illustrated subject index to medical photography, it may be of some value to the uninitiated.

James H. Rothenberger

QUESTIONS AND ANSWERS

FRIGIDITY

To the Editor:—*A 32-year-old woman who has been married 10 years and has two children has never had a feeling of sexual gratification. She has consulted several general practitioners, a prominent psychiatrist, and two gynecologists. Their various treatments have been of no avail. A few years ago an operation on the clitoris was reported as beneficial in such patients. Has this report been confirmed?*

A. Neumaier, M.D., Glencoe, Minn.

Answer.—Definitive therapy for the disturbed family unit described above necessitates knowing whether this woman ever had an orgasmic response to any form of sexual stimulation; whether she experienced successful response to other sexual partners before, or during, the present marriage; whether she reaches a plateau phase, or is limited solely to an excitement phase of response; and whether there is any history of dyspareunia. If there has been dyspareunia its degree, and anatomic distribution should be known. These are a few of the pertinent questions of basic symptomology that must be available before any description of a therapeutic approach could be intelligently presented. The present state of the marriage should be evaluated. This can be effectively accomplished only by a detailed interrogation of both husband and wife. There should also be an adequate evaluation of reasons for the marriage, descriptions of any patterns of basic conflict in interpersonal relationships, or both.

The husband should be interrogated at length as to details of his technique for sexually stimulating his partner; his knowledge of female sexual anatomy; the degree of his concern (if any) with his wife's failure to achieve sexual gratification; whether he has successfully stimulated other partners and if so, what different techniques (if any) were responsible for this success. The wife's answers to these same questions will also be of major importance.

Frequently a family unit history unfolds which describes the husband's bungling attempts to find, or stay with the small overprotected clitoris, as his wife's sexual excitement mounts. The clitoris varies tremendously in size, anatomic placement, and degree of suspensory ligament support. Every effort should be made to train the individual husband to contend satisfactorily with the wife's particular anatomic variant. This, obviously, can be satisfactorily accomplished only by working directly with the family unit and not by use of charts, pictures, or vocalization techniques. It is also important to emphasize that there are many other techniques of successful sexual stimulation other than direct clitoral massage.

Presuming normal sexual awareness and potential physical responsiveness for the female partner, it is now completely possible to train a woman to physical orgasmic response to effective sexual stimulation in those situations where such a response has not been previously experienced. This is a family unit training process and not solely confined to the education of the female partner, but we must be certain that the wife's lack of orgasmic response is primarily on a physical basis rather than a symptom of a family unit psychosexual imbalance. It is important for the physician to remember that the achievement of orgasmic experience is not necessarily the be-all or end-all of a woman's pattern of psychosexual maturity.

The circumcision of the clitoris, an operation performed more frequently in Central and South America than in the United States, has theoretical value only in the relatively unusual situation of a heavy or hypertrophied foreskin completely obtunding a relatively small and insensitive clitoris. Even when dealing with this type of anatomic involvement, there would still be no indication for surgery, unless the woman provided a most satisfactory history of personal manual orgasmic relief of sexual tensions. The history of this operation is one of empirical development of a surgical technique to increase female sexuality from a purely physical point of view. To date, we have not had to consider the operation of clitoral circumcision as indicated surgery.

LIMITATIONS OF FIRST AID

To the Editor:—*What is the best book covering first aid and instructions for the care of persons with illnesses that a layman might use as a guide while on a camping trip in an isolated area, or while confined in a bomb shelter waiting for radioactivity to subside? What would constitute the best medical kit for use under these circumstances?*

R. F. Wettingfeld, M.D., Jamestown, N. Y.

Answer.—The best education for a lay person who faces the conditions described lies in first aid and home nursing. To guide a lay person toward giving definitive treatment, it would be necessary to proceed from readily detectable evidences such as chills, fever, chest or abdominal pain, nausea, and dizziness to specific diagnoses. Such a person

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

would need a variety of medical supplies. No comprehensive authoritative textbook covers the subject for the layman, and it seems unlikely that a simple, helpful one can be written. It suffices for general purposes, however, to know first aid and home nursing, and there is available the excellent "Red Cross Home Nursing Textbook" in addition to this organization's "First Aid Textbook." Perhaps the most important medical conditions to consider here are accidental injuries, vascular episodes, infections, and childbirth. The textbooks mentioned suffice for lay care. The home nursing book contains a section on childbirth, clamping the cord, and massaging the uterus. The Federal Civil Defense Administration has prepared several pamphlets on bomb-shelter medical problems, including "Emergency Action to Save Lives" and a first aid textbook but has decided against preparing a more comprehensive book. People who already are affected with illness or are pregnant should obtain specific advice from their physicians and, if necessary, medication if they foresee a period of isolation. Similarly they should obtain advice if they foresee a specific hazard while isolated. There is no place in this country where medical advice is not obtainable fairly quickly except perhaps in case of a blizzard.

Concerning kits, the problem of preparing a list of needed items is far different when considering illness than when considering accidents. Comparatively few items suffice for an accident kit, in general the items are not perishable, and people can be taught relatively easily how to use them. Medical contingencies may, however, be of innumerable kinds, the occurrence of any of which cannot be predicted, and the lay person cannot readily be taught how to make the diagnosis nor how to use the drugs properly. It would be extremely costly, and probably dangerous, in any case, to advise that lay people equip themselves regularly with even a restricted group of drugs, some perishable, such as paregorics, antibiotics, nitroglycerin, and antihistaminics, for use when isolated. Nonexempt narcotics cannot be prescribed legally except for already-existing conditions. It has seemed unwise, therefore, to prepare for general dissemination a list of drugs for the definitive treatment of medical conditions. It seems likely that the lay person's individual interests are only occasionally best served by recommending medical items beyond those in common household use. Such items should be recommended by the personal physician, who is familiar with the situation to be faced and the person's education, intelligence, and needs. Concerning first aid kits, the "Red Cross First Aid Textbook" and several pamphlets of the Federal Civil Defense Administration contain lists of suggested items. The average first aid kit, containing small dressings, a triangular bandage or two, possibly an antiseptic and a burn ointment, tourniquet, scissors, and tweezers, does not suffice for treatment of some of the major injuries. These might require large-size dressings, at least four triangular bandages, splints, a blanket, a flashlight, and flares. Special situations might necessitate the use of insect repellents, sunburn ointment, thermometer, roller bandage, and adhesive tape. The proper use of these items requires adequate education because there is a possibility of their ineffective or definitely harmful use.

SWELLING OF TONGUE

To the Editor:—*On four or five different occasions in the past two years, either on retiring for the night or on awakening in the morning, and, on one occasion during the night, a patient's tongue became swollen. Twice the patient was helped by subcutaneous administration of diphenhydramine hydrochloride. On the other occasions, chlorpheniramine tripelennamine reduced the swelling. It appears to be an allergic reaction, but I cannot find any definite cause or causes of this condition. On the first occasion the patient awoke with this condition while in a hospital, receiving continuous sacral tetracaine anesthesia for an acute arterial occlusion. After the administration of diphenhydramine he obtained relief within a few minutes. On the other occasions he was at home and not taking any drugs. No other allergic manifestation has been observed. What is the cause and treatment of this condition?*

I. Irving Perlmutter, M.D., Geneseo, N.Y.

Answer.—The prompt administration of antihistaminic drugs without exception has brought relief from the swelling described. Although the tongue has been swollen no mention is made of the occurrence of an associated respiratory embarrassment. The description given would suggest the onset of angioneurotic edema of the tongue. The first episode would suggest that the anesthetic agent then being administered may have been a causative factor. Although allergy to drugs may have been responsible for the initial episode, other factors such as fatigue, tension, bacterial or parasitic infection, or an allergic response to other allergens, particularly ingestants, may have contributed to that and subsequent episodes. A study of allergic factors would probably be of only limited, if any value in the solution of this problem.

The following measures would appear indicated. 1. The patient should avoid the use of a para-aminobenzoic acid type of local anesthesia of the tetracaine group if dental or other indications for local anesthesia should arise. Local anesthetic agents with a significantly different structure, such as lidocaine hydrochloride, usually are well tolerated by persons who are sensitive to the para-aminobenzoic acid category of local anesthetic agents. 2. The patient should carry on his person epinephrine hydrochloride for subcutaneous administration should additional reactions occur. Small amounts of this agent probably should be used against attacks of swelling, despite the history of the vascular disease mentioned. There is a reasonable chance that the swelling in the tongue may extend into the throat and produce respiratory embarrassment. 3. The patient should carry on his person one of the antihistaminic drugs mentioned. This agent should be ingested promptly at the earliest evidence of swelling. 4. It should be ascertained that other medications, such as aspirin or penicillin, have not been used, since allergy to other drugs might contribute to the problem described. Finally, the patient should avoid fatigue and take adequate treatment for any infection.

LACK OF OVARIAN HORMONES

To the Editor:—*After giving birth to her first child, a 25-year-old woman noticed a progressive decrease in the size of her breasts, some irregularity in her menses, and occasional amenorrhea and oligomenorrhea. How can this disorder be corrected?*

P. C. Corrado, M.D., New York.

Answer.—To determine the underlying cause of the oligomenorrhea and occasional amenorrhea more information is needed. Did this patient have any complications after her pregnancy, such as massive hemorrhage or clinical evidence indicating subsequent damage to the anterior pituitary? The pituitary-ovarian axis integrity must be maintained if normal menstrual cycles are to proceed. The decrease in size of the breasts and associated menstrual irregularity imply beginning ovarian failure, which may be due to primary pituitary failure and subsequent ovarian hypofunction. Primary and secondary ovarian hypofunction may be due to a variety of causes. The endometrial state should be investigated to determine whether ovulation is occurring. If endometrial biopsy showed the presence of a secretory phase it would indicate that ovulation has occurred. The recording of basal temperatures would also help indicate whether ovulation is occurring. Several 24-hour urinary assays for gonadotropin would indicate the degree of pituitary activity.

Ovulation occurs only when stimulation by the gonadotropic hormones is exactly right. When ovulation does not occur, it can reasonably be presumed that this sequence is interfered with. Further decrease in ovarian function will eventuate in oligomenorrhea and amenorrhea. Anovulatory bleeding may then be present. The decrease in size of the breasts would be further evidence of ovarian failure.

In an attempt to discover the cause, determination of thyroid function is indicated. Nutritional factors should be explored. Disturbances in these should be corrected. Loss of weight without a proper supplement of the vitamin B complex is an often overlooked factor in menstrual irregularity of this type. After all avenues of investigation have been exhausted, recourse to cyclic therapy with an accepted estrogen given orally for 20 days and supplemented by one of the progestins for 5 days and then repeated for three successive months should be considered.

POSTURE OF SCHOOL CHILDREN

To the Editor:—*What criteria are there for appraising the posture of school-age children? If a child has a poor posture but no skeletal, muscular, or neurological defect, how can the posture be improved?*

Leo F. Gowen, M.D., Webster Groves, Mo.

Answer.—Posture varies with body types and, therefore, heredity as well as with environmental factors. Many postural studies have been made and normal posture could be considered as an average or mean. The individual norm, however, includes a wide range. Variations of posture in a group of children of the same age are great and yet each may have good posture.

The primary school-age period (6 to 12 years) represents the time when individual body types assert themselves. Slight sex difference in growth are manifested during the early part of this period. Lumbar lordosis increases but the abdomen in some may still be prominent as in the preschool-age child. The chest is flat and the thoracic spine is straight though the shoulders may appear rounded. Knees are fully extended when standing but not when running. Mild foot pronation may be present when the child is standing relaxed but may diminish or disappear with walking or running. Structure is flexible and the child may appear double jointed. The latter part of this period is characterized by greater growth in stature and weight in girls.

In the secondary school-age period (12 to 18 years) girls and boys grow at different rates. The former mature faster and develop feminine proportions. The individual variation of masculization and concomitant muscularization in boys is tremendous. The abdomen should by now be flat in almost all children. Other elements except for sexual traits and flexibility are similar to those of the earlier age group.

Good posture denotes an absence of strain or a near relaxation in the erect and sitting as well as the recumbent position. Good posture permits graceful and purposeful movements with the least expenditure of energy. Good posture in the normal child cannot be achieved by braces and "ramrod" exercises. It can be developed by the use of proper diets, clothing, furniture, well-organized sports programs, and physical education. The activities of slowly maturing youths should be greatly restricted if severe strains, sprains, and overfatigue with its dire effects are to be avoided. Above all, we should recognize that tremendous individual variations in normal posture exist and that it is impossible to have a single standard for all children.

LIGHTNING PAINS

To the Editor:—*I have a patient who has tabes dorsalis with severe lightning pains in the legs. The diagnosis is beyond question. He has had treatment with intravenously given arsenic and more recently with 15 million units of penicillin over a two-week period. The pains are beginning to be severely disabling and are interfering with his work as a cab driver and his rest at night: Can you make any suggestions for treatment?*

M.D., Florida.

Answer.—To give relief from the lightning pains of tabes dorsalis has always been a problem, but for the relief of sporadic attacks, frequently precipitated by rapid weather changes and changes in barometric pressure, three daily intramuscular injections of corticotropin gel should prove consistently effective. These patients are not placed on oral steroid therapy during the interim period. For patients who are having frequent attacks, the intramuscular administration of 1 Gm. of vitamin B_{12}, twice a week over a period of several months, at times minimizes the frequency of the attacks. There is no indication for fever therapy and chordotomy should certainly be considered as a last resort. Since these patients can easily become addicted to morphine and its derivatives, these drugs should practically never be used for the relief of lightning pains.

BARBITURATE COMA

To the Editor:—*What is the latest treatment of barbiturate coma?*

Walter Weinberger, M.D., Hollidaysburg, Pa.

Answer.—The modern treatment of barbiturate coma is directed toward avoiding anoxia by the maintenance of a patent airway, removal of secretions from the pharynx and tracheobronchial tree, and an adequate respiratory tidal exchange and minute volume, with use of mechanical respiratory aids and oxygen when necessary. The patient is placed in the lateral decubitus position with the head slightly lower than the feet, and turned hourly. Circulatory shock should be counteracted by administration of whole blood, plasma, or plasma expanders, as indicated, and the blood pressure should be maintained by administration of vasopressor drugs, when necessary. Fluid and electrolyte balance are maintained by glucose and saline infusions. Gastric lavage should be performed to remove any unabsorbed drug which may remain in the stomach for many hours, but this must be done cautiously to avoid aspiration of regurgitated fluids. The former use of analeptics has been abandoned as harmful, and only if respiratory paralysis supervenes are phthalic acid-bisdiethylamide or amphetamine (but not picrotoxin) administered. Digitalis is given for heart failure; and for hyperthermia 3 Gm. of salicylic acid may be given per rectum. To expedite removal of barbiturate from the body, extrarenal measures (intermittent peritoneal lavage or the artificial kidney, if available) may be used, but this is rarely indicated. The use of barbiturate antagonists has also been tried with questionable results. For details as to their use and the general principles of treatment of barbiturate poisoning, the reader is referred to Grollman's Pharmacology and Therapeutics. ed. 4, Philadelphia, Lea & Febiger, 1960, pp. 181-182.

HALLUX RIGIDUS

To the Editor:—*A 44-year-old woman has extreme discomfort due to hallux rigidus of the right foot. Roentgenograms of the foot show spurring in the joint. She can walk fairly well for short distances in "flats" but she cannot wear shoes with heels of any kind without experiencing excruciating pains. What would you advise for relief of this condition?*

Carl O. Keck, M.D., Easton, Pa.

Answer.—Hallux rigidus is often a painful condition, particularly in a woman who may wish to vary the type of shoe she wears from a low slipper to a high-heel dress shoe. The rigidity of the first metatarsophalangeal joint prevents such an extreme of functional motion, and the forced motion causes pain. If the foot problem in this patient is entirely limited to the big toe with marked restriction of motion of the first metatarsophalangeal joint, a Keller operation is indicated; and a satisfactory result may be expected. This operation entails removal of the base of the proximal phalanx of the big toe and removal of the exostosis from the first metatarsal bone, to include not only the medial exostosis but any dorsal or plantar proliferation that may be associated with it.

DROWNING AND RESUSCITATION

To the Editor:—*A recent attempt to resuscitate a person who had been under water for 20 minutes stimulated this question. What is the longest time a person can be submerged and still respond to resuscitation?*

Walter K. Grigg, M.D., Batavia, Ill.

Answer.—Definite information about the length of time of submersion after which successful resuscitation has been achieved in drowning cases is not available. The consensus is that six minutes is the longest period one can survive without incurring permanent brain damage if resuscitation is successful. It is extremely doubtful that resuscitation could reactivate the heartbeat or respirations of a victim who has been submerged for 20 minutes.

WASHINGTON NEWS

House Passes Health Bill . .

Medical Research Hike . .

Democratic Committee Health Views . .

Retired Federal Workers' Insurance . .

Medical School Research . .

Miscellany . .

AGED HEALTH BILL TO SENATE

A major development in the political controversy over health care of the elderly was House passage of a federal-state program to provide care, on a voluntary basis, for aged persons with limited financial resources.

The action was an important victory for foes of such compulsory government medicine schemes as embodied in proposals to include health care financing under the social security system. However, the Senate still had to act, and there was powerful support for a social security approach.

The eventual outcome in Congress was difficult to predict. Should the lawmakers finally pass a social security bill rather than the House plan, it was expected that President Eisenhower would veto the bill. The chief executive has repeatedly stated his opposition to any compulsory health care program.

The House measure—approved by the House Ways and Means Committee—was similar in mechanism to existing federal-state public assistance programs for needy persons. It would cover persons 65 years of age and older who are determined by the states to be unable to afford health care on their own. Any or all of a wide range of proposed surgical-medical-hospital benefits could be provided according to the states' individual programs.

The bill was brought up in the House under a procedure barring any amendments. Thus, there was no opportunity for proponents of social security health bills to seek House passage of their proposals as a substitute.

The legislation went to the Senate Finance Committee headed by Sen. Harry F. Byrd (D., Va.).

LARGE INCREASE IN RESEARCH FUNDS VOTED BY SENATE

Following a pattern of recent years, the Senate topped the House in voting appropriations for federal medical research activities. Despite warnings of a possible presidential veto, the Senate approved $664 million for the National Institutes of Health, compared with the House sum of $455 million and the Administration's request for $400 million—the amount granted last year.

The money bill, one of the last of the session, went to a House-Senate conference to work out differences between the two versions. Odds were a figure somewhere between the two will be agreed upon.

In opposing the increased money grant, Senate Republican Leader Everett M. Dirksen (R., Ill.) declared that "all we have gotten is the expenditure of more and more money over the years, and not results that are commensurate with the expenditures." He said he would ask President Eisenhower to veto such a bill "to stop the business of accepting every project that comes along, irrespective of its real merit."

DEMOCRATIC HEALTH COMMITTEE SETS POLICY LINES

A possible guide to the Democratic Party's platform plank on health during the forthcoming presidential campaign was outlined by the newly formed advisory committee on health planning of the Democratic Advisory Council.

The committee's tentative decision on a sweeping health program, including compulsory health care financing under the social security system, meant that such a program would be submitted to the Democratic convention for approval in July. The committee's task was to draw up a health plank platform for the party.

The committee, headed by Dr. Michael E. DeBakey, Houston, did not endorse any specific measure in Congress, but "in principle" backed the Forand and McNamara bills to provide financing of health care for the elderly through higher social security taxes.

Other points agreed on in principle included: expansion of medical research to reach $3 billion a year by 1970; a White House conference on heart disease and cancer early in 1961; better control of accident prevention, environmental health needs, mental illness and rehabilitation; federal aid to education, including scholarships, new facilities and expansion of present facilities, and a program to provide more teachers.

Another point agreed on in principle called for legislation to require all manufacturers of ethical drugs to be licensed and to give the Food and Drug Administration authority to pass on the efficacy as well as the safety of drugs.

A final point called for the expansion of the Hill-Burton hospital program and a study program to see how hospitals can be used more efficiently with an aim to reducing hospital costs.

(Continued on next page)

RETIRED U. S. WORKERS BILL

Legislation to provide a contributory health insurance program for already-retired federal workers cleared another hurdle with passage by the House Post Office and Civil Service Committee. The measure was similar to a bill approved by the Senate earlier this year.

Congress last year authorized government-wide health insurance programs with federal contributions in order to allow U. S. employees, for the first time, the benefit of contributory plans similar to those in many private industries. However, already-retired workers were not included.

The American Medical Association, among other organizations, had urged Congress to set up some sort of a program under which retired federal workers could participate in a private contributory health insurance plan.

SUPPORTS FUNDS FOR GENERAL RESEARCH IMPROVEMENT

A measure to earmark a percentage of all funds appropriated for federal medical research grants for distribution to institutions for improving their research and research training activities was supported by the American Medical Association.

"In recent years, the federal program of research project grants has grown to such an extent that medical schools and other research institutions are being deprived of a substantial measure of control over the content and direction of research activities carried out in their facilities," said A. M. A. Executive Vice-President Dr. F. J. L. Blasingame.

In a letter to Rep. Kenneth A. Roberts (D., Ala.), chairman of a House commerce subcommittee, Dr. Blasingame pointed out that "the use of project grants has also limited the discretion of medical schools to follow new avenues of research which in their judgment would contribute materially to the development of well-rounded research programs."

Enactment of the measure, which would not involve any additional appropriations, would "restore to the institutions carrying out research programs control of their own destinies. It would also provide the schools with the opportunity to strengthen those projects which do not enjoy great public appeal but which nevertheless may contribute to the improvement of the health of our people."

MISCELLANY

Sen. Estes Kefauver (D., Tenn.), chairman of the Senate antitrust subcommittee studying the drug industry, introduced legislation calling for federal licensing of drug manufacturers. The measure also would require that the Food and Drug Administration pass on the efficacy of new drugs as well as their safety.

More than 127 million Americans had health insurance at the end of 1959, according to a survey of the Health Insurance Council. The council said reports from insurance companies and health care plans showed that 72% of the civilian population had voluntary health coverage; an increase of 4.8 million over the preceding year.

A controversial Treasury Department ruling that might lead to members of professional associations such as the American Medical Association not being able to deduct all their dues as business expenses would be reversed under a measure approved by the House Ways and Means Committee. The Treasury recently held that members of tax-exempt associations would have to pay taxes on whatever portion of their dues or other contributions were used to influence legislation. The bill would continue to allow entire tax deductions on dues.

The Administration asked Congress to authorize a reshuffle of the U. S. Public Health Service to allow establishment of a Bureau of Environmental Health and a National Center for Health Statistics. The Environmental Health Bureau would consolidate all PHS activities dealing with radiological health, and air and water pollution into one section. The aim is to allow the new bureau to concentrate on health dangers in the environment.

The number of deaths from flu and pneumonia was about 60% greater during the first three months of this year than during the same period in 1959, the U. S. Public Health Service reported. The death rate from the two diseases for persons 45 years of age or older nearly doubled. The statistics provided conclusive evidence that the nation suffered "a very severe type of influenza epidemic" last winter, PHS officials said.

Three Public Health Service scientists reported evidence that malaria can be transmitted to human beings by mosquitoes infected with monkey malaria. Most scientific opinion hitherto has been that that type of malaria which infect animals cannot be transmitted to man by an infected mosquito.

The three chief members of a special investigating unit looking into recent charges involving the Food and Drug Administration were named by Secretary Arthur S. Flemming of the Department of Health, Education and Welfare. They were Charles H. Kendall, General Counsel of the Office of Civil and Defense Mobilization; Dr. Charles Austin Doan, Dean of the School of Medicine at Ohio State University and winner of the latest Distinguished Service Award presented by the American Medical Association; and William A. Costello, Regional Inspector for the Internal Revenue Service. Charges were aired before the Senate antitrust subcommittee that there had been some lax administration of federal drug inspection programs.

The Food and Drug Administration announced seizure of 311 pounds and 145 capsules of the habit-forming drug peyote at coffee shops in the Greenwich Village area of New York City. Peyote, a cactus-like herb, can only be sold under a physician's prescription. Apart from habituation, no harmful effects have been reported, though there is no information the drug serves any medicinal purpose.

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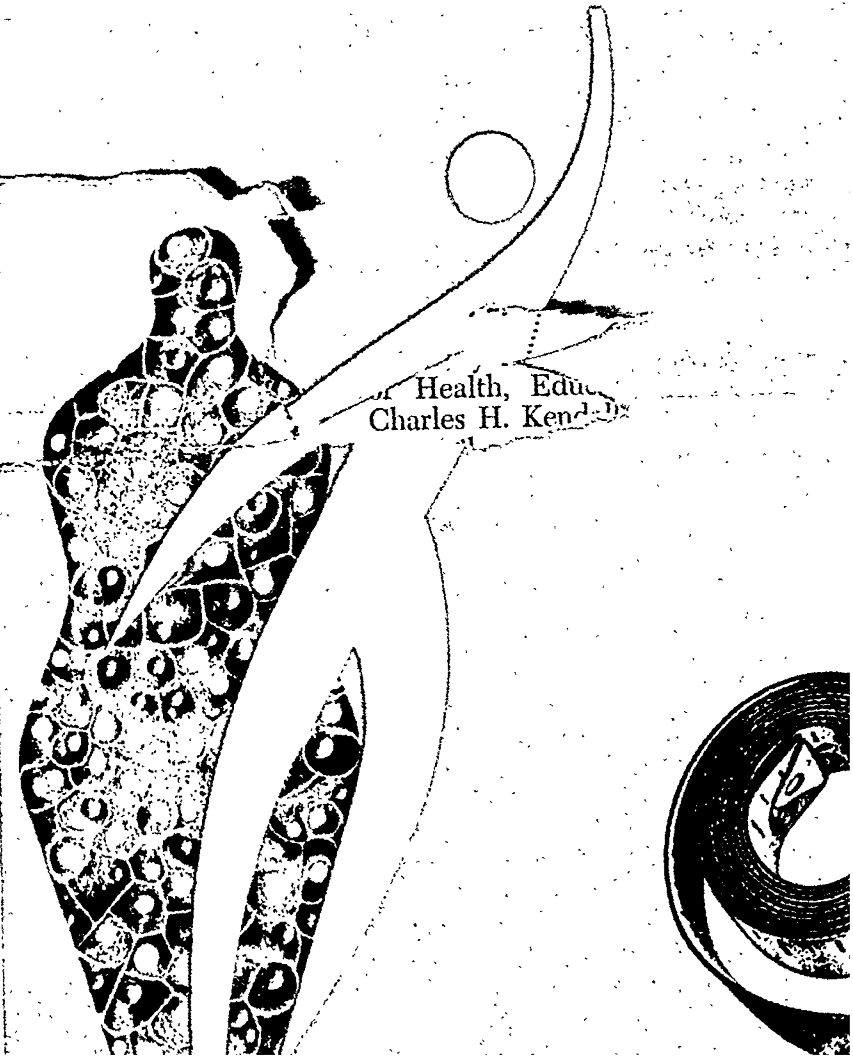

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MEDICINE—THE DECISIVE DECADE

PRESIDENT'S ADDRESS

E. Vincent Askey, M.D., Los Angeles

IT is characteristic of inaugural speeches to point to the challenges which lie ahead or to mention the threshold at which we stand. I wish that I could depart from this time-honored tradition. Certainly nothing would give me more pleasure than to tell you that I view the future without misgivings and that I see nothing ahead but clear sailing and fair winds.

The truth is that I do not.

I believe that the next ten years will comprise medicine's decisive decade.

I believe that medicine will encounter line squalls, veering winds, and rough waters.

I believe that we do stand at the threshold.

Arnold Toynbee, the great British historian, has observed that the course of nations throughout history has been determined by their response to the challenges of their time.

I believe the same observation applies to the medical profession.

We are challenged to prove, once again, that medicine practiced in a free society is the most effective medicine; that the physician's full potential can best be realized if he is allowed, as an individual, to treat his individual patients in an individual way; that the doctor is not, and cannot become, an organization man whose organization is government; that the art of medicine may depend upon science, but remains an art; and that art, placed on the assembly line, is quickly stifled.

We must prove these things conclusively.

No one else can prove them for us.

No one else will.

We must prove these truths for the sake of our profession. But more important, we must prove them for the sake of 180 million Americans, whose stake in our success overrides every other consideration.

These people are our patients. They deserve the best medical care we can give them. They are accustomed to receiving it. They must continue to get it.

During the past ten years, we have thrown back a series of frontal assaults on medicine's freedom to practice without government interference. Suppose, if you will, that we had lost our fight in 1950. National compulsory health insurance would now be ten years old.

Forgetting its cost in dollars, which would have been astronomical, let us think of its cost in terms of effective practice.

During the fifties, one scientific advance followed another at breakneck speed: new drugs, new vaccines, new techniques, new victories.

As rapidly as science developed these new tools, we put them to use. We moved quickly because we were free to move quickly. We rode the great wave of scientific progress because we were not held back by the dragging anchor of governmental restriction.

The result is apparent: the healthiest nation in the world's history.

Thinking back on this past decade, I believe that it was characterized chiefly by a tightening of the bonds between art and science.

From research laboratories came a profusion of new tools: fiberoptics; radio-isotopes; the magnificent, versatile drugs we use in chemotherapy.

The biologists are even probing the mysteries of the cell and of the genesis of life itself.

We discover, more each day, that the chemistry of living humans, despite their general similarities

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Read before the 109th Annual Meeting of the American Medical Association, Miami Beach, Fla., June 14, 1960.

in pattern, is as different as fingerprints. And slowly we learn to identify these differences—patient by patient—in easier, simpler ways.

The bond between physician and patient has been strengthened immeasurably as a result.

Yet, it is ironic that at this very moment, when our capacity for individualized treatment is heralding a revolution in medical care, the pressures mount heavier to force us into the adoption of assembly line methods.

Those who favor this approach seem to believe that the doctor can function—as effectively as ever—as a cog in a governmental machine.

But there is a great difference between a good cog and a good doctor. A cog must turn as the wheel turns, for it is totally dependent. A cog must mesh, obedient to the machine of which it is a subordinate part. A cog can exercise no judgment, can demonstrate no skill, can deviate to no appreciable degree from its prescribed function. A cog must conform, or the gears are stripped.

No, good doctors make bad cogs; and good cogs become bad doctors.

It is equally true that no governmental machine ever devised can crank out mass cures for mass illnesses through mass production methods.

But let us not deceive ourselves: The urge to automate medicine intrigues many.

The health professions are being told that only the Federal Government can solve the problem of providing health and medical care for the aged.

Medicine, it seems, is being held at fault for its own success.

I mention the health care of the aged because it is the most immediate pretext for an aggression against the free practice of medicine. It is a flank attack—not a frontal assault—by the proponents of compulsory national health insurance, but it is nonetheless dangerous.

There are now more than 15 million people over 65 years of age in the United States.

The medical profession sees this as a blessing, not a burden, for the citizens of this nation.

But the increasing life expectancy of the population demands that the country as a whole readjust some of its outmoded attitudes toward aging. The phenomenon of longer life demands that Americans think clearly and plan soundly for the future.

Instead, the problems which go hand-in-hand with aging are being thrown into the political arena.

It is a pity. An understandably confused nation is being led to believe that political nostrums can cure medical and sociological ailments. And nothing could be further from the truth.

Only 15% of elderly persons are on old age assistance. An undetermined number, although able to finance other costs, find it difficult to withstand the additional financial burden of serious illness. These are the people for whom something should be done.

They constitute a relatively small minority, however; for most of those over 65 now finance their health care adequately or receive it as indigents covered by some government program.

Unfortunately, many in position to deal with the problem are more worried about the voting potential of the majority than the unarguable need of the minority. And they seek support from those naive enough to believe that they can get something for nothing from government.

Let us make no mistake about it: there are many who would like to intrude upon the medical profession, now and in the future. The events of this past decade suggest it. The events of the present confirm it. The events of the future will depend on medicine's ability to meet the challenges ahead.

We shall do so successfully, but only if our patients will stand with us and only if every doctor in this country realizes that he not only has the right, but the responsibility, of speaking up in behalf of his patients.

It is not going to be enough for the individual physician to give tacit support to the efforts of his local and state societies or to those of the American Medical Association. He must be more than a dues-payer if he wishes to preserve medicine's freedom to practice in its traditional way.

He must be the articulate voice of his profession, wherever he is. He must be dedicated to the well-being of his community. In matters of health, he must be willing to assume responsibility and discharge it as the expert he is. He must be citizen as well as doctor, plaintiff's attorney for his patients, missionary for the individual and for the individual's rights.

Difficult, yes. Impossible? No.

Medicine has been thrust into center stage during these past 10 years and will remain there during the next 10. The American people who comprise the audience are, for the most part, appreciative of our efforts. But do not forget that the critics are also present and that they are powerful and vocal.

Our shortcomings in the years ahead—and we shall have them, being human—will be dissected and scrutinized. Yet our accomplishments will be equally apparent as medicine stands in the spotlight.

Let us not, through any sense of false modesty, underplay them.

I am not suggesting that the physician become Main Street's version of the man in the gray flannel suit. But I am suggesting that each individual doctor must concern himself with what Madison Avenue would call the "image" of the medical profession.

That image is simply an extended likeness of himself and his colleagues, reflected in the mirror of public opinion. It can be warm and sympathetic or cold and impersonal. It can be changed for the better or changed for the worse; but at any given moment, it reflects reality.

I am saying that actions speak louder than words; that words are without value unless they are backed up by deeds; that the image of our profession is the reflection of our substance and not our shadow.

I am saying that—rightly or wrongly—the American people demand more than our scientific skills.

Medicine cannot be practiced under controlled, laboratory conditions. It belongs as much on the crowded street as it does in the ivory tower.

Medicine is based, true enough, on the physical sciences. But the practice of medicine sets off a chain reaction in the social sciences, the results of which—whether they be economic, political, or sociological—must then affect medicine itself.

As we enter this new and challenging decade, let us take a moment for self-appraisal.

Each year the art of medicine depends more and more upon science. More tools are being placed at our disposal than my generation ever dreamed of. In our preoccupation with those tools, is it possible that we are forgetting something?

Are we forgetting that a physician must be more than a skillful person who applies science to the treatment of disease?

I hope we are not, for medical care is not complete without the warmth, understanding, and human concern of the doctor. We deal with individuals who fear, hope, sorrow, and worry. We must retain our ability to allay fear, to inspire hope, to ease sorrow, to strengthen the patient's determination to get well. Those who went before us worked wonders with very little, but the traditional black bag, with its limited contents, was wonderfully versatile in the hands of a warm and sympathetic physician.

Let us never forget that the doctor must always be counsellor and friend.

My next question is this: does the medical profession receive the credit it deserves? The answer, I think, is unquestionably that it does. We deserve credit—and get it—for the contribution we have made to longer and healthier lives for Americans. We deserve credit—and get it—for the quality of medical education in this nation and for our constant efforts to improve it. We receive credit—and deserve it—whenever we pitch into a community health problem and solve it.

This is the plus side of the ledger. There is also a minus side.

It seems to me that we talk too much to ourselves, and too little to the nonmedical members of our communities. As an example, we say that medical care is available to everyone, regardless of ability to pay for it, and discover that millions of Americans have failed throughout the years to get the message.

We know that the cost of medical care is a matter of deep concern to many of our patients. We know why costs are higher. Who can explain it better? Furthermore, who will explain it if we do not?

On matters of this sort, let us anticipate the public's worry and recognize not only its interest in knowing the answers but also our responsibility to supply them.

Finally, there is the matter of our twofold duty. We must not only be physicians, but citizens as well.

Many of us tend to delegate too many of our personal responsibilities to our medical societies or our civic organizations. This is especially true in a political sense. What happens in our local governments, in our statehouses, and in our nation's capitol is not only important to the physician as a member of the medical profession but also to the physician as a citizen of the United States.

In my view, it is the duty of the individual doctor to make his viewpoint known to the representatives he helps elect to office and it is his duty to speak out, in behalf of his profession, in matters affecting health.

It is not enough that he work constantly to upgrade his knowledge and sharpen his skill as a physician. It is not enough that he labor long and hard to help his patients. It is not enough that he strive always to improve the quality of care provided by the hospital on whose staff he serves.

As hard as the physician works at these essential tasks, he must somehow find time to do more.

In matters of health he must be his community's leader, voice, and conscience.

Whether the problem involves the understaffing of a county hospital, the need for modernizing a mental institution, or the improvement of a school health program, the physician must assume the responsibility which is uniquely his.

He has tried—and tried hard—in the past.

He must redouble his efforts in the future.

For if he does not, the leadership he is now free to assume will pass, by default, to others unqualified to handle it.

We live in a time when two opposing forces contend for supremacy within the nation.

One force believes that the most governed are the best governed; that the individual cannot, or will not, act effectively on his own; that the nation's progress can only be assured if Americans walk in lock-step under the watchful eyes of government.

The other force believes, with Lincoln, that government should do for people only what people cannot do for themselves. It believes that responsible individuals, working freely together, can accomplish anything they put their minds and muscles to.

Finally, they believe that the individual stride is longer and faster than the pace of the lock-step and that it will carry us further along our way.

The medical profession finds the choice easy and obvious.

Effective medicine flourishes only in the temperate climate of liberty.

In the decisive decade before us, we are challenged to prove by our deeds our right to the trust reposed in us by the American people.

The stakes are high. The times move quickly.

Let us, as doctors and citizens, prove beyond argument our ability to meet the challenges in the years ahead.

MATERNAL DEATH DUE TO DISSEMINATED VARICELLA

Stewart A. Fish, M.D., Dallas, Texas

Four fatal cases of chickenpox occurring during pregnancy are reported. Each patient died of characteristic diffuse interstitial pneumonitis. This complication of varicella has been described previously and, from the data available, it does not appear that there is any special susceptibility to disseminated chickenpox during pregnancy. At present, there is no drug therapy available which will cure the disease or modify its course once the lungs and other viscera are involved. Treatment is directed toward maintaining adequate pulmonary exchange and water balance until the disease resolves spontaneously. In none of these four cases did the infant survive.

It has gradually become evident that varicella (chickenpox), which is usually a mild childhood disease, may cause severe systemic complications and death in adults. When disseminated varicella occurs, the lungs are almost always involved by a characteristic, diffuse, bilateral, interstitial pneumonitis. In addition, the pleura, gastrointestinal mucous membrane, kidneys, brain, liver, and other vital organs may be affected by the disease process.

It is the purpose of this report to emphasize the potential seriousness of varicella in adults and to review four instances of maternal death due to chickenpox which have occurred in Texas during the past several years.

Report of Cases

Case 1.—A 24-year-old woman (gravida 2, para 1), who was four months pregnant, first noticed the appearance of a rash on her trunk, arms, and scalp on Feb. 12, 1956. She suspected that this was chickenpox since her 3-year-old child was convalescing from this disease. On the next day she developed a distressing cough. A physician was consulted; he prescribed tetracyclines, without examining the patient. On Feb. 14 the cough became much worse, and shortness of breath developed. This was soon followed by cyanosis, hemoptysis, and cramping, lower abdominal pains. At this point the patient was admitted to the hospital, and it was evident that she was acutely ill. Her medical history was uncomplicated; she had been vaccinated for smallpox as a child. A chest x-ray, taken one year prior to admission, showed normal findings. On physical examination her temperature was 102 F (38.9 C); pulse regular, about 120 per minute; respirations, 40 to 50 per minute; and blood pressure, 120/60 mm. Hg. The skin of the face, neck, scalp, upper arms, back, chest, and abdomen was covered with many unilocular, nonumbilicated papules and vesicles which were typically varicelliform. There were only a few chickenpox lesions on the lower extremities. Several shallow ulcers were present on the tongue, buccal mucosa, soft palate, and the uvula. There was no lymphadenopathy. Crepitant rales and bronchial breath sounds were audible over the left upper chest posteriorly. The heart was not enlarged. The abdomen was slightly distended, and bowel sounds were hypoactive. The uterus was enlarged to the size of a four-month pregnancy. Vaginal examination disclosed a bloody discharge from a closed cervix. The findings of a rectal examination were normal. The hemoglobin level and leukocyte count were within normal limits. An x-ray of the chest disclosed an extensive, bilateral, diffuse pneumonitis.

The patient was immediately placed in an oxygen tent and given tetracycline intravenously. Despite the use of oxygen, the patient's cyanosis persisted. She coughed frequently, expectorating a foamy but tenacious, blood-tinged sputum. During severe paroxysms of coughing she would become disoriented and much more cyanotic. She received a narcotic in small doses every four hours to control the cough. Her vital signs continued to be the same as on admission, and at 6:30 p. m. on Feb. 14 she expelled a four-month fetus and the placenta, without excessive hemorrhage. The next morning her condition was relatively unchanged. Examination of the chest disclosed many crepitant inspiratory and expiratory rales and wheezes in both lungs. Cyanosis and dyspnea persisted, and her respirations were rapid and grunting in nature. She was given aminophylline by slow, intravenous drip, but her condition remained essentially unchanged until 9:30 p. m. when her heartbeat became very rapid and irregular. She died suddenly thereafter.

The postmortem examination revealed that the patient's skin was involved with an extensive vesiculopapular polymorphous hemorrhagic rash. Eosinophilic intranuclear inclusion bodies were found on microscopic examination of the skin lesions, which confirmed the diagnosis of chickenpox. Similar lesions were also found in the esophagus, pleura, lungs, spleen, liver, and bladder. There was noted, also, an extensive, diffuse, bilateral bronchopneumonia, which was interpreted as primary varicellar pneumonitis. In addition, pericardial effusion, acute tracheobronchitis, acute toxic nephrosis of the kid-

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From the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical School, and the Committee on Maternal Mortality, Texas Medical Association.

Read before the Texas Association of Obstetricians and Gynecologists, Austin, Texas, Feb. 13, 1960.

neys, and central softening of the adrenals were among the findings.

Case 2.—A 19-year-old woman (gravida 1, para 0), who was approximately 18 weeks pregnant, was well until May 1, 1958. Then she developed a skin rash, which was interpreted by her family as chickenpox. This was accompanied by the development of a persistent cough. She was afebrile and did not feel particularly ill. On May 4 the cough became worse, and the patient developed dyspnea and cyanosis. At the same time, she began to have intermittent, cramping, lower abdominal pains, and the physician in attendance felt that the patient was about to abort. At 8 p. m., May 4, she was referred to a local hospital and, on arrival, expelled a four-and-one-half-month fetus and the placenta. There was minimal bleeding. On physical examination, the patient was cyanotic and dyspneic. Her respiratory rate was 60 per minute; temperature, 104 F (40.0 C); pulse, 120 per minute; and blood pressure, 100/70 mm. Hg. The heart was normal except for tachycardia. Both lungs were clear of abnormal physical signs. The uterus was tightly contracted, and there was no bleeding from the vagina. The hemoglobin level was 14 Gm. per 100 cc., hematocrit value 45%, and white blood cell count 38,000 per cubic millimeter. No other laboratory data were obtained.

Shortly after admission, her blood pressure fell to 70/40 mm. Hg. The patient was given 500 cc. of whole blood with levarterenol bitartrate and her blood pressure returned to 100/70 mm. Hg. About one hour later, she again went into shock and was given another 500 cc. of whole blood, in addition to a liter of normal saline solution. Her hypotension did not improve, and, at 4:30 a. m., May 5, she became acutely dyspneic and cyanotic. Her blood pressure fell to 50/0 mm. Hg. and her pulse rose to 160 per minute, while respiration remained 60 per minute. A chest x-ray was taken, which showed an extensive, bilateral, diffuse pneumonitis. Shortly thereafter the patient developed hemoptysis, and numerous rales were heard in the lungs. From the time of admission the patient had received about 2,100 cc. of intravenously given fluid; at this time she was given another liter of dextrose containing levarterenol bitartrate. Large doses of aqueous penicillin, streptomycin, and intramuscularly administered tetracycline were also given. At about 8 a. m., 12 hours after admission, another 500 cc. of dextrose and water containing four ampules of levarterenol bitartrate was given to maintain her blood pressure. Her condition was not significantly improved, and it was observed that she had had no urinary output since admission. Her condition continued to deteriorate, and at 6 p. m. her blood pressure dropped to an unobtainable level. A tracheotomy was performed, but, despite further attempts at resuscitation, the patient died shortly thereafter.

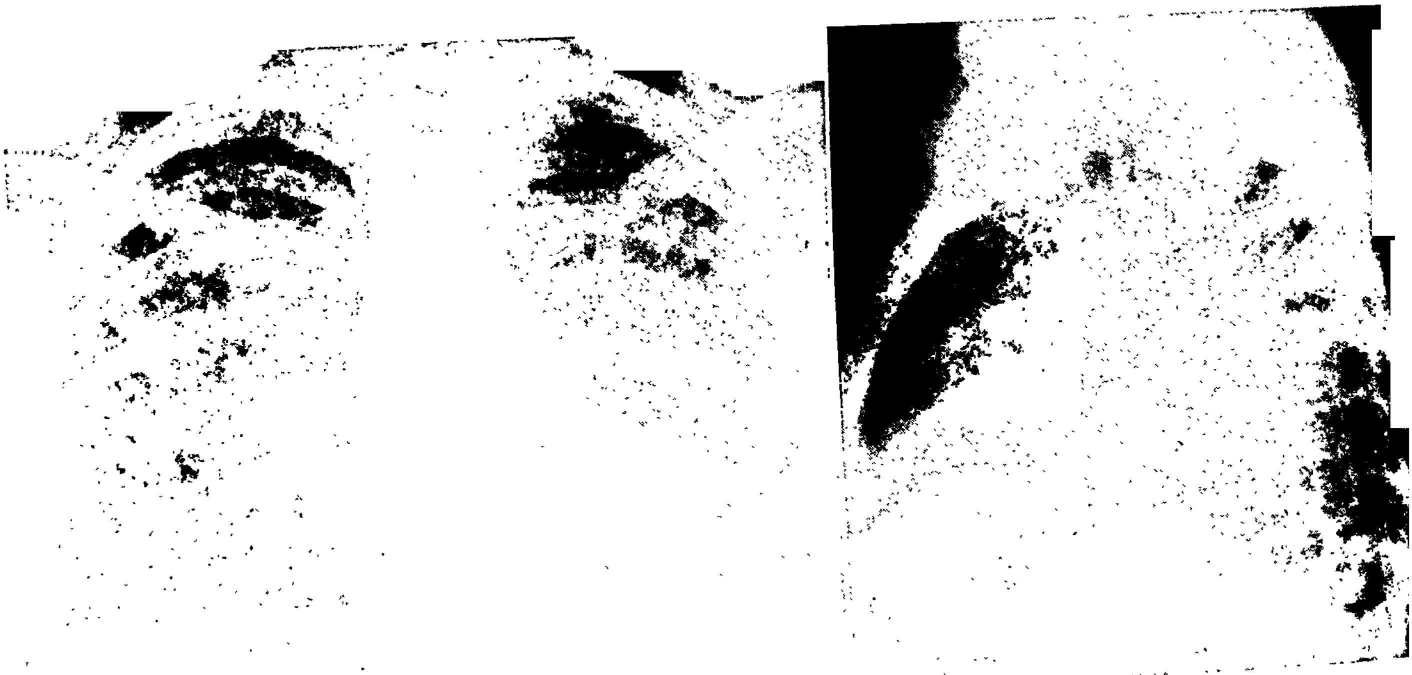
At autopsy an extensive, superficial, vesiculopapular polymorphous skin rash was found, which was consistent with the clinical diagnosis of chickenpox. Eosinophilic intranuclear inclusion bodies were found on microscopic examination of the skin lesions, confirming the diagnosis. There was noted, also, a diffuse, bilateral, interstitial pneumonitis, with a large amount of pulmonary edema present. In addition, there was marked focal glomerulonephritis. Cultures of the blood and pulmonary fluid were taken at the time of postmortem examination, and a light growth of hemolytic Staphylococcus aureus was obtained.

Case 3.—A 26-year-old woman (gravida 5, para 4), was first seen on Dec. 5, 1957. She was thought to be pregnant, and her estimated date of delivery was Aug. 15, 1958. Her obstetric history was uncomplicated; she had had four previous normal spontaneous deliveries. She was in good health except for the residual effects of paralytic poliomyelitis in her left leg; the poliomyelitis occurred in 1955. Her pregnancy was uneventful up to the last week of July when her husband called the attending physician stating that one of the children had chickenpox. On July 31 the patient notified her physician that she also had chickenpox. The next day she was seen by her physician and was found to have a temperature of 104 F. (40.0 C), and a vesiculopapular polymorphous skin rash, with the typical centripetal distribution of varicella. She was given oleandomycin and a cough medicine together with instructions for general care, and she was allowed to return home.

On Aug. 3 her husband called the physician to report his wife's cough was much worse. At that time she was also short of breath and her temperature was 102 F (38.9 C). By telephone, the physician prescribed a combination of tetracycline and novobiocin calcium in addition to a narcotic for the cough. About two hours later the patient's husband called to inquire if the medicine would make the patient drowsy. The answer was affirmative, and the husband was instructed to call back if anything changed. About two hours later the husband again called the physician and said that he thought his wife was dead. The doctor immediately went to the home and found this to be true. There was no evidence of fetal or maternal heartbeat, and no attempt was made to deliver the baby. Permission for an autopsy was refused. A blood culture, done immediately after death, failed to produce any growth.

Case 4.—This 23-year-old woman (gravida 3, para 2), whose expected date of delivery was Aug. 15, 1959, had a normal pregnancy until May 6, when she noticed a skin rash on her chest, scalp, and arms. During the next two days, she developed fever, cough, gradually increasing dyspnea, and hemoptysis. On May 9 she became cyanotic and severely dyspneic and was admitted to the hospital. Her medical history was noncontributory except that she had been exposed to chickenpox by her two children, within the preceding three-week period. The patient had never had chickenpox but had been vaccinated for smallpox as a child. On admission, examination disclosed an obese, acutely ill patient whose uterus was enlarged to the size of a six-month pregnancy. There was a vesiculopapular polymorphous skin rash present, with the typical centripetal distribution of varicella. Her temperature was 99.6 F (37.5 C); pulse 106 per minute; respirations 30 per minute; and blood pressure 122/40 mm. Hg. There were numerous fine scattered rales over both lung fields. Marked cyanosis and dyspnea were present. The patient's hemoglobin level was 14.2 Gm. per 100 cc., and the white blood cell count was 6,800 per cubic millimeter, with a normal differential count. The results of urinalysis were negative except for evidence of dehydration. On the chest x-ray there was evidence of a bilateral, diffuse, mottled pulmonary infiltration, without signs of consolidation or fluid (see figure).

During the patient's first 48 hours in the hospital her pulmonary condition improved slightly with the use of humidified intermittent positive-pressure oxygen, intravenously administered tetracycline, cortisone, and fluids given intravenously. However, on May 11 oliguria, melena, and hematemesis developed; and the patient's hemoglobin level fell to 9.7 Gm. per 100 cc. She was then treated with blood replacement and limited fluids given intravenously. It was thought that the hematemesis and melena were from intestinal involvement with chickenpox and the oliguria was secondary to renal tubular necrosis from anoxia. There was no evidence of blood coagulation defect at this time. On May 14 her pulmonary state became somewhat worse; large sheets of bronchial epithelial cells were found on sputum examination. Only a few bacteria and leukocytes were seen. A light growth of coagulase-positive Staphylococcus aureus was obtained on culture. During the subsequent five days she became anuric; she continued to require oxygen, repeated small blood transfusions, and constant careful management of her fluid and electrolyte balance. Cortisone therapy had been discontinued, and erythromycin was given. On May 21 the patient had a spontaneous delivery of a living, premature female infant, which died in about four hours. There was no excessive bleeding. Subsequently, the patient continued to be anuric and cyanotic, and the melena persisted. An extracorporeal hemodyalisis was performed on May 23 in an attempt to correct her electrolyte imbalance. However, her condition gradually deteriorated, and she died on May 24. Permission to perform an autopsy was refused.



Chest x-ray of patient (case 4) showing characteristic, diffuse, interstitial pneumonitis due to chickenpox.

Disseminated Varicella

Clinical Features.—The clinical characteristics of disseminated varicella have been fully described elsewhere,[1] and no attempt will be made to present in detail all the various ramifications of this syndrome. The salient clinical features of disseminated varicella are as follows: 1. The patient is almost always an adult who has been vaccinated for smallpox but who never had chickenpox. 2. The typical vesiculopapular polymorphus skin rash of chickenpox appears approximately 14 to 16 days after exposure. 3. Evidence of systemic involvement appears on the second or third day after eruption of the rash. Respiratory symptoms are the first and most serious to occur. There is rapid progression from a persistent cough to hemoptysis, dyspnea, tachypnea, and cyanosis. 4. Physical examination of the lungs may result in normal findings, but fine scattered rales, with occasional rhonchi and wheezes, are heard more commonly. Other physical findings in the early stages are compatible with any severe exanthem. 5. Laboratory studies disclose a normal or slightly elevated white blood cell count, with no significant left shift. Sputum and blood cultures are negative as are all agglutination studies. Superinfection with bacterial contaminants may occur later in the course of the disease. 6. Roentgenographic examination of the chest shows a characteristic diffuse, fine nodular infiltration throughout both lung fields without evidence of consolidation.[2] The extent of the pulmonary infiltration and the clinical seriousness of the disease are directly related to the severity of the skin rash. In nonfatal cases clinical improvement occurs much more rapidly than the disappearance of the pneumonic infiltration which may persist from six to ten weeks. 7.. The mortality among patients with disseminated chickenpox has been estimated to be between 10 and 30%.[1i] When recovery occurs, there are usually no sequelae.

Pathology.—In the two cases in which autopsy was performed, there was swelling, proliferation, and desquamation of the pulmonary alveolar septal cells. The cellular exudate was chiefly mononuclear. There was a large amount of fibrinous material seen throughout all sections of the lungs. Eosinophyllic intranuclear inclusion bodies, identical to those found in the skin lesions, were seen in the alveolar septal cells. In both cases, the kidneys were characterized by areas of marked fibrinoid necrosis of the glomerular tufts, consistant with the diagnosis of acute toxic nephrosis. Clinically, there was renal failure and intestinal involvement in case 4, but, unfortunately, an autopsy was not performed.

The pulmonary and renal changes as described in these cases are identical to those which have been reported elsewhere in cases of disseminated chickenpox.[3] The pericardium, esophagus, pleura, bronchi, spleen, liver, and bladder were also involved in case 1, and similar findings have been described in other autopsy studies.[1h]

Treatment.—The therapy of disseminated chickenpox is difficult to evaluate. There is no antibiotic that is specific for this disease; the major role of antibiotics, in this instance, is in the prevention and treatment of secondary bacterial invasion. Cortisone and its derivities are ineffective in decreasing the seriousness of the disease process. There is apparently little that can be done to alter the predetermined course of the disease if there is extensive involvement of the lungs, kidneys, or other vital organs.

The major therapeutic effort should be directed toward the maintainence of an adequately humidified pulmonary exchange, in addition to the prevention of any superinfection by bacterial contaminants. DiMase, Grover, and Allen[1i] have recently pointed out the value of the tank-type respirator in the management of the acute stage of varicella pneumonitis. Their results suggest this technique should be used in the patient with severe pulmonary involvement. The importance of maintaining careful fluid and electrolyte balance must also be emphasized.

In the first case reported here, the respiratory exchange was very poor when the patient was first seen; she failed to respond to the available treatment. In case 2, it was apparent that excessive fluids were given intravenously, and the resultant pulmonary edema contributed significantly to this patient's death. In case 3, the seriousness of the patient's condition was not recognized by the physician, and she failed to receive proper medical attention. In case 4, the systemic complications were managed satisfactory; however, there apparently was irreversible renal damage which failed to respond to all of the available resources.

Comment

There is apparently no specific tendency or increased susceptibility to chickenpox during pregnancy. In about 66 cases of disseminated varicella reported since 1942, the sex distribution is fairly equal; the association with pregnancy is probably coincidental.

It is not generally appreciated that chickenpox in adults is a potentially fatal disease. Awareness of this fact should bring about earlier diagnosis of cases of disseminated varicella with pneumonitis and, as a result, an improvement in the prognosis for such cases.

The true incidence of varicella pneumonitis is not presently known; it has been advised[1e] that routine chest x-rays be performed on all adult patients with chickenpox. There is certainly ample justification for this suggestion.

Furthermore, a plea is made for earlier hospitalization of patients with disseminated varicella; this was not accomplished in any of these four cases until the patient was obviously desperately ill.

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LATEX PARTICLE SLIDE TESTS IN RHEUMATOID ARTHRITIS

COMPARATIVE STUDY

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Two rapid latex particle slide tests used in rheumatoid arthritis, the RA-test and the eosin slide test, were compared with the latex fixation test, here used as a standard of reference. Of the total group of 309 persons tested, 290 (94%) showed either all negative or all positive results with the three methods used. In the remaining 19 patients (6%) positive results were obtained on one or both slide tests, while the latex fixation test result was negative. In all cases in which positive results were obtained with the latex fixation test, the slide test results were also positive. Either slide test can be considered a satisfactory screening procedure if due care is exercised in their interpretation.

Many serologic tests for rheumatoid arthritis are in wide use. The nature of the reactions and their significance with regard to pathogenesis are under investigation by a range of testing procedures.[1] Other methods have been described as simple rapid tests suitable for screening purposes and readily applicable under any circumstance. Among the latter are the RA-test, a patented kit procedure which will be described, the bentonite flocculation test,[2] and the less well known slide latex fixation test, hereinafter referred to as the eosin slide test.[3]

It was our purpose to evaluate the RA-test and the eosin slide test in terms of their practicality, sensitivity, and specificity as compared to the latex fixation test.[4] Their role in epidemiologic survey work for rheumatoid arthritis was examined from the viewpoint of number of reactors among specially selected groups of nonrheumatoid patients.

It is currently held that the tests involve the reaction between a gamma globulin found in the serum of rheumatoid arthritics, called the "rheumatoid factor," and normal gamma globulin from other sources, either human or animal, called the "reactant." The reaction is usually demonstrated by permitting rheumatoid serums to clump particles coated or "sensitized" with reactant. The immediate mechanisms continue under study and have recently been thoroughly reviewed.[5]

Materials and Methods

The patient populations from which the serums came included adult patients from the outpatient department and inpatient service of King County Hospital, a large city hospital dealing exclusively with indigent people; hospitalized, exclusively male patients of Seattle Veterans Administration Hospital; and, as controls, college students of the University of Washington.

The series was divided into five groups for analytic purposes. Group A included 65 patients who met the American Rheumatism Association's criteria for classic (18 patients) or definite (47 patients) rheumatoid arthritis, not including the serologic response as one of the criteria.[6] Because of the nature of the population from which they were selected, patients considered probable or possible by the criteria were so infrequent as to make their inclusion in the series noncontributory.

The patients in group B presented a variety of pathological states which have been categorized as connective tissue disease. Included were two syndromes often considered to be variants of rheumatoid arthritis, ankylosing spondylitis and arthritis accompanied by psoriasis. The spondylitic patients all had unequivocal, roentgenographically demonstrable sacroiliac disease. Most did not have peripheral joint disease of, for example, knees, elbows, or hands. All the psoriatic patients had arthritis of several joints, indistinguishable from rheumatoid arthritis, and could not be included in a narrowly defined category of psoriatic arthropathy manifested only by distal interphalangeal joint involvement and the characteristic, roentgenographically demonstrable, destructive lesion. Those with rheumatic fever had active, acute disease. The patients with systemic lupus erythematosus had positive findings of L. E. cell preparations as well as typical manifestations such as nephrotic syndrome and serositis; none had chronic deforming arthritis.

Patients who did not have generalized connective tissue disease but were referred to an arthritis clinic made up group C, those with musculoskeletal diseases. The largest proportion had gout or degenerative joint disease.

The disease patterns represented by the patients in group D, selected disease states, were specifically chosen in an effort to enhance, if possible, the number of false-positive slide test results. Early experience suggested that serums from patients with diffuse neoplastic disease and hyperglobulinemic states would often be found to give positive results on the slide tests. The serums from patients diagnosed as having idiopathic hyperglobulinemic purpura of Waldenström came from our clinic and, through the kindness of their physicians, from two recently reported cases.[7] The serums described as

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hyperglobulinemic showed globulin contents of 4.5 Gm.% or more. These were determined as the difference between the total serum protein and the serum albumin not precipitating with 27% sodium sulfite, the protein determinations being made with a modified Weichselbaum biuret reagent.[8] By this method the normal serum globulin concentration was 2.88±0.43 Gm.%.

Group E was composed of equal numbers of healthy male and female college students. They represented a population sample in no way comparble to the patient groups tested except that exactly the same serologic techniques were applied to both.

Serums were separated and stored frozen at −20 C. Checks failed to reveal changes in the test results when fresh serums were compared to repeatedly frozen and thawed specimens from the same bleeding. Samples were not inactivated before the test. Each test was carried out independently and its result was read and recorded by number without knowledge of the other two results.

The latex fixation test (hereinafter referred to as F II LP, abbreviated from fraction II latex particle[9]) was performed in glycine-saline buffer solution at a pH of 8.2. Lyophilized Cohn fraction II was made up as a 1% solution in buffer, heated at 63 C for 10 minutes,[10] and stored at 4 C. Latex particles averaging 0.810 μ in diameter were received as a stock suspension. This was progressively diluted with distilled water until 0.1 ml. of the diluted suspension added to 10 ml. of water gave a light transmission of 7 to 13% in a standard 1-cm. cuvette in a Beckman DU spectrophotometer at a wavelength of 650 mμ. The initial test serum dilution was 1:20, and serial twofold dilutions were made to a total of five tubes. The results were read with the naked eye after 90-minute incubation at 56 C after overnight storage at 4 C and centrifugation. Agglutination at a dilution of 1:160 or greater was recorded as "positive." Prozone phenomena were not observed.

The eosin slide test was carried out by adding two drops of the stock suspension of latex to a well-mixed drop containing equal amounts of test serum and a 1% solution of eosin in distilled water on a clean glass slide. No biological reagent other than the test serum was used. The result was read within three minutes after the slide was tilted sufficiently to allow thorough mixing. Negative results showed a smooth pink appearance, closely resembling that of cream of tomato soup, while the positive reactions produced a stippled granular appearance, particularly obvious when the suspension was watched while flowing across the slide. Delay in the reading beyond three minutes was found to result in a higher percentage of positive reactions.

The RA-test was performed as specified in the accompanying directions. The reagent is said to contain latex particles and a gamma globulin preparation. A drop of this suspension was mixed on a glass slide with a drop of test serum diluted 1:20 with glycine-saline buffer solution. The result was read instantly as positive if the even, cloudy suspension was converted to a clear solution containing scattered clumps or floccules.

Results

The results are summarized in table 1. The population of rheumatoid arthritics (group A) examined belonged to a heterogeneous group exemplified by long duration of disease (mean 16 ± 11 years), advanced aged at the time of testing (mean 50 ± 17 years), an unusually high proportion of men (48% not including the four patients from the Veterans Administration Hospital), and a relatively good functional level, 90% attending an outpatient clinic. It was noted that careful laboratory studies, including biopsies and synovial fluid examination of patients with diagnostic problems, often resulted in their categorization as exhibiting "classic" disease despite atypical clinical presentation.

TABLE 1.—*Results of Three Agglutination Tests for Rheumatoid Arthritis*

Group	Cases, No.	Number Positive		
		F II LP	Eosin Slide	RA-Test
A Rheumatoid arthritis ....total	65	53	57	58
Classic	18	14	14	15
Definite	47	39	43	43
B Connective tissue disease ....total	50	3	5	7
Rheumatoid spondylitis	21	1	1	2
Arthritis with psoriasis	6	...	1	2
Acute rheumatic fever	10	...	...	...
Lupus erythematosus	4	...	1	1
Periarteritis nodosa	1	...	...	...
Dermatomyositis	1	1	1	1
Scleroderma	1	1	1	1
Reiter's syndrome	6	...	...	...
C Musculoskeletal diseases ....total	89	3	9	6
Degenerative joint disease	21	1	1	1
Gout	25	1	6	4
Idiopathic hydrarthrosis	4	...	...	...
Myositis, bursitis, and tendinitis	7	...	...	...
Musculoskeletal infections	7	...	1	...
Shoulder-hand syndrome	2	...	...	...
Miscellaneous	23	1	1	1
D Selected disease states ....total	55	16	18	18
Neoplastic, with hyperglobulinemia ....total	20	7	7	7
Multiple myeloma	6	...	...	...
Leukemia	7	2	2	2
Carcinoma	7	5	5	5
Neoplastic, without hyperglobulinemia ....total	11	2	3	3
Multiple myeloma	2	...	1	1
Leukemia	5	1	1	1
Lymphoma	2	...	...	...
Carcinoma	2	1	1	1
Hyperglobulinemic states ......total	24	7	8	8
Hepatic cirrhosis	11	4	5	5
Idiopathic purpura	3	3	3	3
Miscellaneous	10	...	...	...
E Controls ....total	50	1	1	1
Grand total	309	76	90	90

Eighteen patients (11 men and 7 women) had nodules, 4 of them showing splenomegaly with leukopenia; 14 had a positive result with F II LP, including 3 of the latter 4. Three patients had a juvenile onset; tested as adults, two showed positive results.

Twelve patients had a negative result with F II LP; eight were characterized as definite and four as classic, all the latter showing nodules. Slide tests carried out on the serums of these 12 patients were positive in 6 cases: 3 with both tests, 1 with the eosin slide test only, and 2 with the RA-test only.

The connective tissue disease category as a whole (group B) showed few positive reactions although the patients with scleroderma and dermatomyositis tested reacted to all tests. Clinically, a striking feature was the general lack of agglutinating activity in the serums of the patients with psoriasis. Typical rheumatoid arthritic patients with classic joint manifestations plus a few irregular patches of psoriasis routinely showed negative agglutination reactions. Excluding the patients having scleroderma and dermatomyositis, one subject showed a positive result with F II LP as contrasted to three positive results of the eosin slide test and five positive results with the RA-test.

In group C the results were comparable to those in group B, with a low percentage of positive reactions, the slide tests being positive two to three times more frequently than the F II LP. The greatest discrepancy of this type was found in those with gouty arthritis.

About one-third of the specially selected patients in group D showed agglutinating activity. Uniformity of reactivity among the three tests was observed, in contrast to the discrepant reactions found in several of the aforementioned groups. Four patients with disseminated bronchogenic carcinoma were included in the neoplastic group; all showed positive agglutination test results. None had hypertrophic pulmonary osteoarthropathy. Two patients, serums with relatively uncommon monocytic leukemia (Naegeli type) were reactive.

Table 2.—*Practical Factors in Three Agglutination Tests for Rheumatoid Arthritis*

	Test		
	Standard Latex	Eosin Slide	RA-Test
Time required	18 hr.	3 min.	Instant
Biological reagents	Fraction II globulin	None	Supplied with kit
Test serum required, ml	0.1	0.1	0.05
Equipment	Laboratory	Office	Office
Cost	++++	+	++
Ease of interpretation	Easiest	Easy	Moderately subjective

The single positive reactor in group E was an asymptomatic 18-year-old woman in good health with a negative family history; all three tests had positive results. The proportion of positive results in this small control group was consistent with the results of the eosin slide test alone in a study of 1,000 normal college students, 3% of which were positive.[11] The combined findings suggested approximately equal sensitivity of the three tests in a young, healthy population.

Factors affecting the practicality of the three tests are presented in table 2. The slide tests are well suited to routine office use or epidemiologic work; the F II LP, permitting some quantitation as expressed by titers, is better suited to investigational needs. Although the ease of interpretation is perhaps the most important practical consideration, its evaluation is difficult and is subject to the experience of any one laboratory.

Comment

In the total group of 309 patients tested, 290 or 94% showed either all negative or all positive reactions with the three methods used. In the remaining 19 patients (6%) discrepant reactions were encountered; in all of these cases one or both of the slide tests had positive results, while the F II LP had a negative result. We have not encountered a single specimen showing a positive result with F II LP which did not give positive results with both slide tests. Either slide test can be considered a satisfactory screening procedure.

The F II LP has been used in this series as the standard of reference, and the results with it conform to those of other investigators.[12] In the well-established rheumatoid population examined, 81% showed positive reactions. Twelve patients (19%) failed to react. These negative reactors seemed to fall into two groups: four with relatively early (mean duration 4 ± 4 years) and active disease and eight with long-standing (mean duration 22 ± 8 years), often severely crippling, but now relatively inactive disease. The former may go on to develop positive serologic reactions, although the work of Calkins and co-authors [13] suggests that they may have a more benign disease process. With regard to the negative reactors with long duration of disease, it seems unlikely that they always reacted negatively; their negative status may represent a reversion from an earlier positive state as the disease subsided to an inactive state. More prolonged and wider experience will be required to establish this hypothesis. DeForest [14] has suggested that serologic reactivity varies with disease activity.

Turning to the false-positive reactors, 23 nonrheumatoid subjects had positive reactions to F II LP. Sixteen of these were among the cases deliberately selected to enhance positivity (group D) and are considered separately. The remaining number of false-positive reactors (7 out of 189; 4%) is consistent with those found in many clinical series. None of the seven showed hyperglobulinemia. Three had diagnoses within the spectrum of connective tissue disease.

The specially selected group D patients tested with F II LP presented a contrasting result. Almost one-third (16 out of 55; 29%) were false-positive reactors. The six patients who had multiple myeloma with hyperglobulinemia reacted negatively, presumably because of the monodisperse nature of the excessive serum protein. Excluding patients with myeloma from consideration, one-half (7/14) of the hyperglobulinemic patients with neoplasia reacted positively, while one-quarter (2/9) of the directly comparable neoplastic group without hyperglobulinemia showed reactivity.

Patients with both hepatic cirrhosis and the idiopathic hyperglobulinemic purpura of Waldenström showed a generalized increase in globulins. The former disease has been studied in some detail with regard to the presence or absence of the rheumatoid factor.[15] Patients with the latter disease, a questionable diagnostic entity, uniformly showed strongly positive reactions. The consistently positive results found in hyperglobulinemic patients with bronchogenic carcinoma and monocytic leukemia constituted an unexpected finding which deserves further study.

As noted, 19 patients had positive reactions to either one or both slide tests, with negative reactions to F II LP tests, and on the basis of this finding the slide tests were considered more sensitive. Six of these reactors were group A rheumatoid patients, which suggested that these simple tests constitute a better diagnostic tool. However, the remaining 13 patients fell into the nonrheumatoid category and are therefore considered false-positive reactors. Thus, while improving on the sensitivity of the F II LP by 10% (6 of 65 rheumatoid subjects), the slide tests resulted in 5% more false-positive results (13 of 244 nonrheumatoid subjects) than the F II LP, an unacceptable increase in terms of diagnostic error.

One finding stands out as unusual; the high incidence of patients with gouty arthritis who had positive reactions to the slide test has not been noted by previous investigators. The differential diagnosis between gouty and rheumatoid arthritis can often be difficult; in some instances the coexistence of the two diseases has been postulated.[16] Four of these patients had an episodic arthritis which responded to colchicine and was associated with hyperuricemia; the other two had hyperuricemia, roentgenographically demonstrable cystic lesions, and atypical arthralgia.

Among the 44 hyperglobulinemic patients of group D, 14 had positive reactions to the F II LP, leaving 30 negative reactors. Only 2 of the 30 had positive reactions to the slide test. Thus, although hyperglobulinemia appears to enhance the number of positive results with the F II LP, little further increase is to be found with the more sensitive slide tests. Their greater sensitivity, therefore, cannot be ascribed to the effects of nonspecific hyperglobulinemia. This conclusion is supported by serum protein analyses of 11 discrepant reactors from groups B and C, only 2 of whom showed hyperglobulinemia.

Comparison of the two slide tests shows little to choose between them. Among the 19 discrepant reactors, 9 had positive reactions to both tests and 5 each were positive on one test alone. Both tests are feasible, in terms of office practice, for screening purposes. No attempt has been made to evaluate the tests as diagnostic procedures in that their role in cases in which there is a diagnostic problem has not been evaluated. The considerable number of false-positive results suggests that due care must be exercised in their interpretation.

Conclusions

The eosin slide test and the RA-test are more sensitive but less specific than the latex fixation test (F II LP). Since all F II LP reactive serums gave positive reactions with both the slide tests, either of these rapid tests constitutes a highly effective screening method. The more frequent false-positive results with the slide tests cannot be ascribed to nonspecific hyperglobulinemia.

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OSSIFIED SUBPERIOSTEAL HEMATOMA

OBSERVATIONS ON THREE INSTANCES INCLUDING ONE IN AN EXTINCT RUMINANT, THE IRISH GIANT DEER

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A female infant aged 6½ months had several hemorrhagic manifestations, including a swelling and ecchymoses on the lower part of the left leg. Initial studies revealed a fracture of the tibia; later studies revealed extensive calcifying bone which surrounded almost the entire tibial shaft. Similar lesions were seen in a human bone believed to be about 150 years old and in a fossil bone from a deer that is believed to have lived about 15,000 years ago. In each case the lesion has the appearance of an ossified hematoma, the space between bone and periosteum being filled initially with blood which is later invaded by osteoblasts. Since the lesion so closely resembles bone sarcoma, the differential diagnosis is important.

Ossified subperiosteal hematoma, although a relatively infrequent pathological condition of bone, almost always causes grave anxiety when diagnosed in the human patient. The present account demonstrates three examples of this lesion. Further, since comparative studies afford a means of acquiring precise ideas of the biological mechanisms of life by enlarging fundamental views of the animal economy, the inclusion of observations on ossified subperiosteal hematoma in the fossil bone of an extinct ruminant species is considered instructive. The most remarkable feature of this bone is the preservation of the heterotopic osseous architecture over a period of 15,000 years.

Demonstration 1

Ossified Subperiosteal Hematoma in Human Patient.—During the 15-year period, 1942-1957, one patient with an established case of ossified subperiosteal hematoma was admitted to the University of Minnesota Hospital. The patient, a 6½-month-old female infant, was one of a pair of fraternal twins allegedly born two or three weeks prior to the date of expected confinement. No history of birth injury was admitted. The other twin had developed normally and weighed 18 lb. (8.2 kg.) at the time of the patient's admission. In contrast, the patient had exhibited some degree of physical and mental retardation and weighed 12 lb. (5.4 kg.) on admission. Save for this slow development, the infant's health had been generally good. Eleven days prior to examination, the patient had passed tarry stools. On the ninth preadmission day, the patient was reported to have vomited blood. On the seventh day prior to admission the lower part of the patient's left leg became swollen and ecchymotic, without apparent reason. Two days later the patient received a mild blow to the left side of the head and developed numerous markedly ecchymotic areas. The parents maintained that the child had received an adequate dietary intake, including vitamin C.

Physical Examination.—Physical examination revealed a rather undernourished infant, 6½ months of age, with a temperature of 99.8 F (37.7 C). The patient refused to sit up, did not follow well with her eyes, and seemed to be generally retarded in physical and mental development. There was a subsiding ecchymotic area over the left frontal parietal region of the skull. The upper lip was lacerated, and an ulcer with mild inflammation of the mucous membranes was noted in the sulcus between the upper lip and the maxillary mucosa. The liver edge was palpable 2 to 3 cm. below the right costal margin. The spleen was not enlarged. Findings of examination of the chest and heart were normal. Small palpable lymph glands were present in all regions. The left lower extremity revealed a large swollen, indurated ecchymotic area in the upper portion of the left lower leg. A complete study for a possible bleeding tendency was undertaken. Results of studies including platelet count, bleeding and clotting time, prothrombin time, and vitamin C content were normal. There was no evidence of a blood dyscrasia. A mild anemia responded to a single transfusion of whole blood.

Roentgenographic Examination.—Initial studies revealed a vertical oblique fracture of the proximal end of the left tibia, with slight anterior displacement of the proximal tibial epiphysis. Streaks of increased density may have represented soft tissue markings due to considerable swelling in this area. Reexamination at a later date presented the findings illustrated in figure 1. Extensive calcifying bone is seen to surround almost the entire tibial shaft. The amorphous appearance of the calcification is characteristic of ossified hematoma.

Comment.—This case demonstrates exceptionally well a calcifying subperiosteal hematoma of the left tibia. Much discussion was provoked in an endeavor to elicit the underlying etiology of the bleeding tendency and of physical findings, without success however. In consultation the orthopedic staff were of the opinion that no definitive treatment was indicated at the time of the patient's admission. The

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possibility of a follow-up study of the infant was precluded by her transfer to a distant state on discharge from hospital.

Demonstration II

Ossified Subperiosteal Hematoma in 150-Year-Old Human Bone.—The case history of the subject from whom this bone was taken is unknown. The specimen (illustrated in fig. 2 and 3) is a human femur dating from the early years of the 19th century and is an exhibit preserved in the Museum of Pathology, at the Royal College of Surgeons, in Dublin, Ireland. Attention should be focused on figure 3 which demonstrates both sagittal sections of the longitudinally divided bone. It is clear that there was no previous fracture injury at this site. The true subperiosteal location of the abnormal bone deposit is demonstrated.

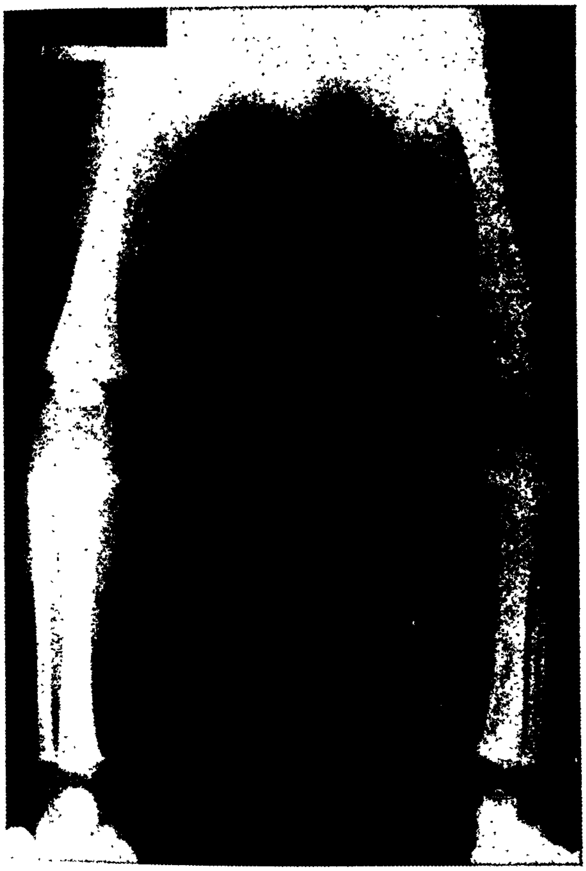

Fig. 1.—Roentgenogram, showing ossifying subperiosteal hematoma of left tibia in infant aged 6½ months.

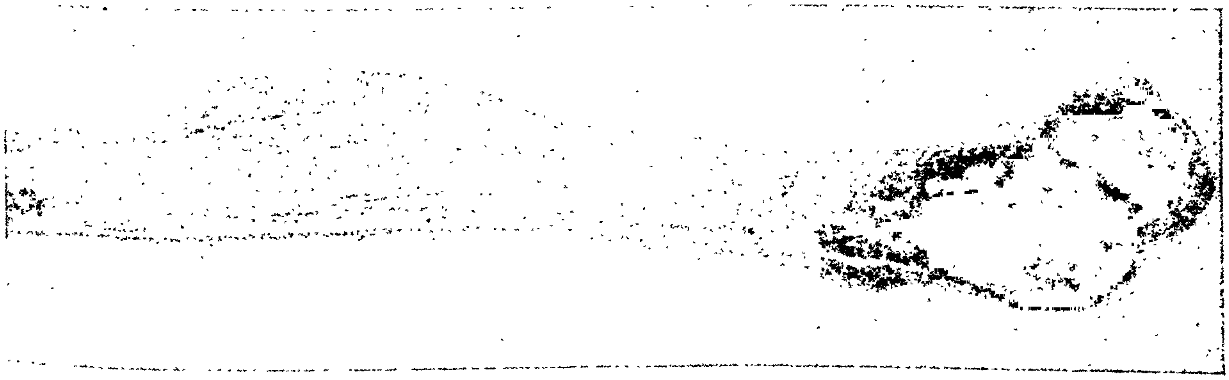

Fig. 2.—Photograph, showing ossified subperiosteal hematoma of human femur dating from early 19th century: history unknown. (Courtesy of Museum of Pathology, Royal College of Surgeons in Ireland, Dublin.)

Demonstration III—The Irish Elk

The term "Irish elk" is a misnomer applied to a large extinct animal species, not an Alces or elk, but a true deer or Cervus, also variously named Cervus Giganteus, Cervus Megaceros, and the Giant Irish Deer. First recorded observations on the remains of this animal date from 1588 and appear as a drawing and description of the head of the Giant Deer disinterred from the ancient lacustrine deposits of County Meath in Ireland and set up first at Rathfarnham Castle, County Dublin. An early written account was a description by Molyneux in 1697, of a fine skull with antlers found at Dardistown, near Drogheda, Ireland. In a paper remarkable for the time at which it was written, Molyneux showed clearly that the antlers were not in any way related to those of elk, but, believing the American moose (an animal he had never seen and was imperfectly acquainted with) to be distinct from the elk, he referred the Irish bones to that species. In 1830, John Hart,[1] a member of the Royal College of Surgeons in Ireland and a lecturer in comparative and human anatomy in the Medico-Chirurgical School in Park Street, Dublin (one of the earliest centers of anatomic instruction in the British Isles), wrote a semblance of an authoritative account on the description of the fossil deer in Ireland to which he attributed the name Cervus Megaceros (fig. 4).

In stature this great deer stood 6 or 7 ft. (1 m. 52 cm. and 1 m. 78 cm., respectively) high at the withers, with the tip of the antlers reaching an estimated 12 ft. (3.5 m.) from the ground. Although little evidence is available, it would seem probable that the Megaceros was not of European but of Siberian origin. The deer, which abounded mostly in Ireland, undoubtedly reached that country from Scotland (where it does not appear to have been plentiful) through the Isle of Man. Other remains have been found in Denmark, France, Germany, Austria, northern Italy, and as far eastward as the caves of Altai in Siberia.

The bone lesion demonstrated in the fossil bone of the Irish elk admirably illustrates that the biological responses to injury in all forms of animal life probably have varied little in the last 15,000 and possibly 50,000 years. The observations reported formed part of a more elaborate investigation of several osteodystrophies encountered in the excavated fossil bones of this extinct deer, some pathological conditions of which have been reported.[2] Figures 5 and 6 illustrate the metacarpal or cannon bone, which, although massive in size, being the equal of and generally larger than the human tibia, is one of the lesser bones of the extinct Irish deer. As in analogous bones in human beings, it is dependent. No evidence of previous fracture is demonstrable. Both gross morphologic and roentgenographic studies well illustrate the area on the shaft of abnormal bone exostosis.

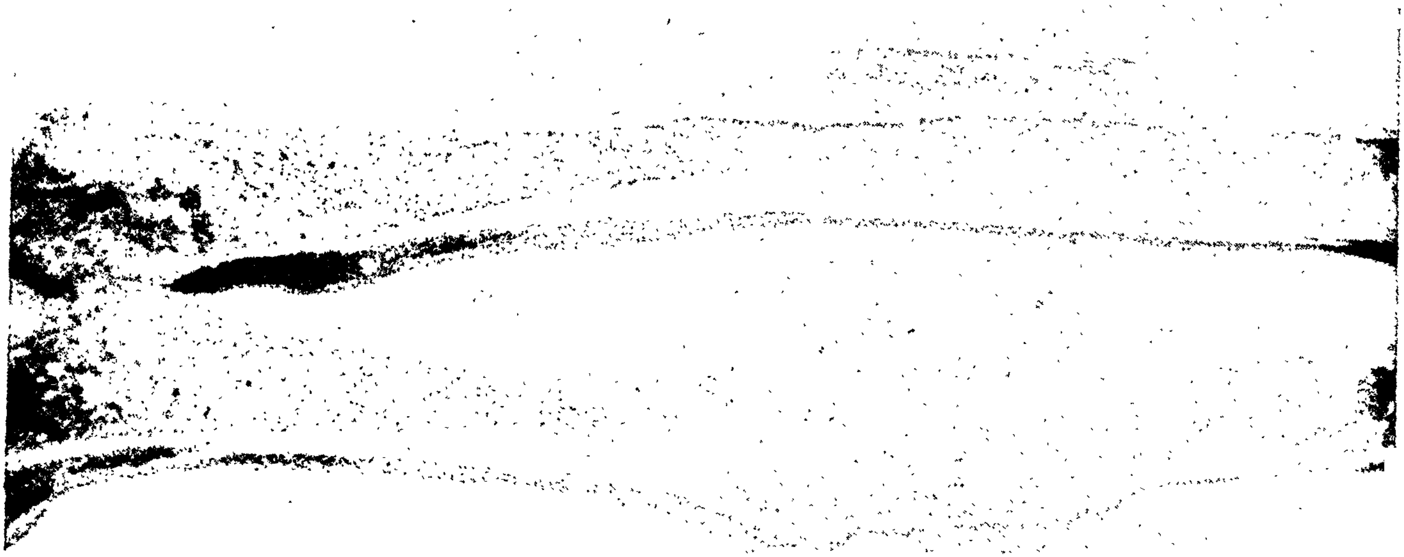

Fig. 3.—Photograph, showing longitudinal section through human femur illustrated in fig. 2, to demonstrate absence of a line of fracture. True subperiosteal nature of lesion is clear.

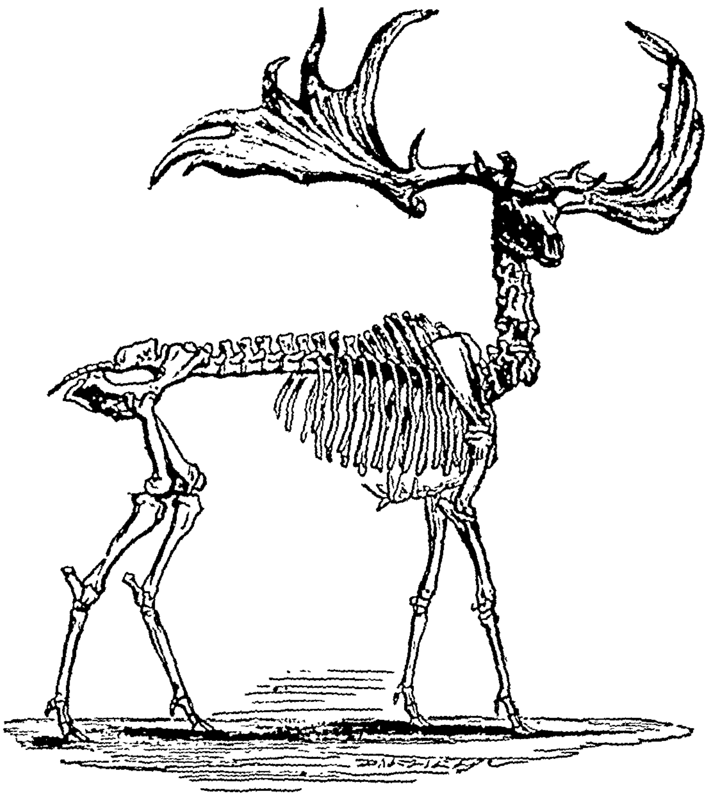

Fig. 4.—Drawing (after Hart,[1] 1830), illustrating extinct Irish elk (Cervus Megaceros).

Comment

Ossified subperiosteal hematoma is an uncommo lesion. Pancoast[3] (quoted by Eliason) found in 16 000 cases of bone operated on only 12 examples this pathological condition. Moreover, variabl terminology to some degree confuses the literatur that is available, myositis ossificans, traumatic ossifying hematoma, and aberrant exostosis havin been used in the past to designate the same condition.[4]

From a practical viewpoint the lesion is of importance to the clinician, roentgenologist, and surgeon since it bears enough resemblance to sarcoma to provoke a great deal of anxiety. Indeed, over one-half the reported cases of ossified subperiosteal hematoma have been misdiagnosed as sarcoma.[5] Frequently, a history of injury may be available and roentgenographic studies may reveal a shadow that increases in size for 8 to 10 weeks before the condition subsides. Not infrequently, however, sarcoma accompanies trauma, to which it may be a rapid sequel, and it is for this reason that several examinations over a period are mandatory. When an established diagnosis of ossified hematoma is made, treatment rarely requires surgical intervention, unless loss of function is involved.

The precise etiology of the condition has not been established. In general, it has been suggested that traumatic injury (as from a kick or a violent fall) may cause the periosteum to be stripped from the bone, the space between the two tissues being filled with blood. The hematoma thus formed is subsequently invaded by osteoblasts detached from the periosteum and the lesion ossifies. Occasionally, subperiosteal hematoma results as a bone lesion in connection with infantile scurvy, which circumstance was the prime suspect in demonstration 1. Commonly the lesion occurs in youth (usually before 30 years of age), most cases being in the group aged 10 to 15 years, and seldom, if ever, in advanced age. Demonstration 2 is of especial interest in that it emphasizes the human femur as a site of pathology. Baetjer and Waters [5] reported 17 cases in adults. Sixteen occurred after multiple injuries at football and one after the kick of a mule; all on the anterior shaft of the femur; and in one-half the cases a clinical diagnosis of sarcoma was made. Brailsford [6] was unable to record improvement in diagnosis, his own studies several years later similarly emphasizing the misdiagnosis of the condition.

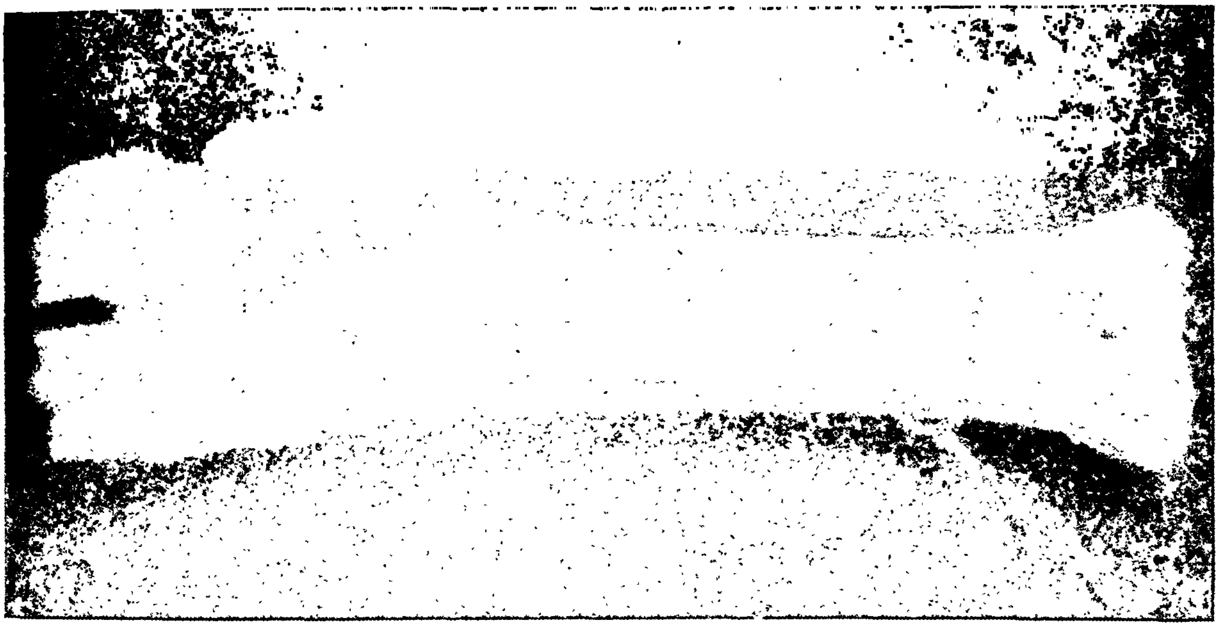

Fig. 5.—Photograph, showing metacarpal (cannon bone) of extinct Irish elk, demonstrating ossified subperiosteal hematoma. Architecture of this lesion has been preserved no less than 15,000 years.

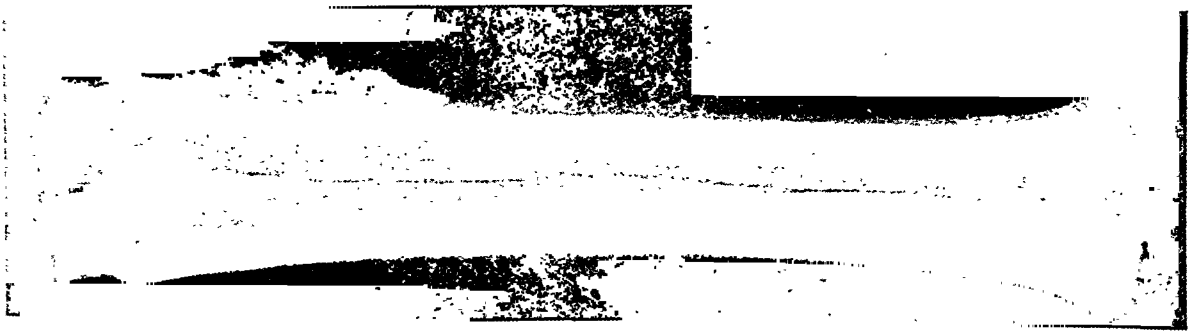

Fig. 6.—Roentgenogram of metacarpal bone of extinct Irish elk, showing abnormal bone exostosis (ossified subperiosteal hematoma) near area of distal digital articulation. No evidence of past fracture of bone.

From the viewpoint of comparative anatomy and pathology the finding of this ossified lesion in the fossil bone of an extinct ruminant is highly instructive. Foremost to appreciate the value of such studies was the founder of comparative anatomy and paleontology, the French zoologist and geologist, Baron Le Cuvier (1769-1832). It is of interest that this celebrated investigator's observations on the Irish elk (Cervus Megaceros, Megaceros Hibernicus) are to be found in his monumental work entitled "Ossemens Fossiles," vol. 12, *Annales du Museum D'Histoire Naturelle.* Animals of the deer tribe being foraging beasts and addicted to kicking, it is not surprising to find an ossified subperiosteal hematoma in a dependent bone, because, with the lesser opportunities that such an animal would have to rest or immobilize the limb, abnormalities in repair and ossification might reasonably be anticipated. In man the ribs, when not immobilized, most closely demonstrate a resemblance to repair in animals. Divided by a barrier of difference both in species and time, the circumstances of similarity in bone repair in contemporary man and in an extinct ruminant lends itself perhaps equally to philosophical and clinical speculation.

Of similar fascinating moment is the evidence furnished by skeletal remains that disease is much older than man himself. A pathological specimen of a dinosaur (Apatosauros), whose age must be measured in millions of years, was discovered by Prof. Roy Moodie in Wyoming with a bony tumor in the caudal vertebra. From the evidence available at the time of writing, it is unlikely that primitive man and Megaceros were coeval in Ireland. The total absence of human implements or remains in the clays in which the fossils of the giant deer are found makes it more than probable that the deer antedated man in that country. Of the animal remains excavated so far, incontrovertible examples of osteoarthritis and lesions resembling those of hypertrophic pulmonary osteoarthropathy in addition to ossified subperiosteal hematoma have been examined by myself in the course of studies on the Irish giant deer.

Summary

Two instances of ossified subperiosteal hematoma, one in a living infant and the other in a human femur dating from the early years of the 19th century, were compared to a similar lesion in the fossil bone of an extinct ruminant species. Features of heterotopic bone architecture characteristic of this lesion are shown in illustrations.

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The author's former teachers, Prof. M. H. O'Connor, Professor of Pathology, (member), and Dr. Henry Stokes, F.R.C.S.I., O.B.E. (past-president), Royal College of Surgeons in Ireland, Dublin, placed at his disposal bone specimens discussed in this study, and provided the stimulus to pursue the comparative investigations afforded by recovery of these fossil bones from the Irish bog.

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EPIGLOTTITIS

REPORT OF THIRTY-SEVEN CASES

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Epiglottitis in children is generally abrupt in onset and often progresses from the first symptoms to a fatal respiratory obstruction in four to six hours. Most patients in the present series came to the hospital with fever and leukocytosis, but the gravity of their condition was not always proportionate to the extent of the leukocytosis. Of the 37 cases here reported, 20 (54%) occurred in boys, and 31 (84%) were in children between the ages of 1 and 5 years. Two patients were dead on arrival at the hospital, and one died within a few hours after admission; the mortality was 8%. Histories of the three fatal cases are given to illustrate the necessity of constant observation of the patient, the abrupt onset of respiratory obstruction, and the place of tracheotomy in management of the disease. Tracheotomy was carried out to prevent asphyxiation in 12 (34%) of the 35 patients who were treated in the hospital.

Few medical emergencies are as urgent as respiratory obstruction, one form of which is epiglottitis. Sinclair[1] in 1941 called attention to this disease entity when he reported on a series of 10 patients. Subsequent series have been reported, but through the years relatively little has been written about epiglottitis. Briefly stated, it is a disease of preschool children characterized pathologically by localized inflammation and edema of the epiglottis and clinically by rapid onset and progression, culminating in respiratory obstruction. It is accompanied by a significant mortality. The disease is easily recognizable, and virtually all deaths are preventable. It seems worthwhile, then, to review local experience with epiglottitis, its pathophysiology, some of the pertinent literature, and current modes of therapy.

Pathophysiology

Understanding of the disease and modes of therapy will be facilitated by an understanding of the mechanism of respiratory obstruction. Knowledge of the earlier stages is not available, and the patho-

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logical course is inferred from clinical examinations in hospital patients and examinations of postmortem specimens.

Figure 1 shows diagrammatically the progression of epiglottic edema leading to obstruction. Postmortem specimens have shown inflammatory changes in the epiglottis (fig. 2), and this can be recognized clinically as intense redness and edema. As the edema increases, the epiglottis is curled posteriorly and inferiorly; a cross section of the epiglottis would present a "horseshoe" appearance. This enlarged epiglottis rests immediately superior to the glottic chink, reducing its effective aperture. If there is any remaining mobility of the epiglottis, inspiration draws it down and further reduces the glottic chink, while expiration tends to blow the epiglottis off, giving a somewhat larger glottic chink during expiration.

With this borderline glottic chink, a bolus of tenacious mucus, such as is abundant in the oral pharynx of these patients, can easily obstruct the remaining glottic orifice, giving complete obstruction. Tracheotomy is the only remedial measure at this time.

Case Material

The material reviewed here is from 37 patients with acute epiglottitis who were admitted to the Children's Orthopedic Hospital in Seattle during the period July, 1950, to July, 1959. These include ward and private patients, and treatment was administered by a number of physicians on the hospital staff. Two of the patients were dead on arrival at the hospital, leaving a balance of 35 patients who could be improved by therapy. As noted in figure 3, 31 patients, or 84%, were between the ages of 1 and 5 years. Of the total number of patients 20 were male and 17 were female, and there was no significant difference in age distribution between the two sexes. This ranged from 5 months to 7 years, three of the patients being under 1 year of age; namely, 5, 6, and 9 months of age. The incidence was seasonal, with 20 cases, or 54%, occurring in the four months between March and June. The remaining months showed an almost equal distribution. Sinclair [1] and Miller [2] also reported a seasonal incidence; however, in their reports the predominant season was autumn. During the first four and one-half years of the period of study, only eight cases were reported. During this same period, there were about 16,000 inpatient admissions, giving an incidence of about 1 patient with epiglottitis for every 2,000 inpatient admissions. During the last four and one-half years of this study, there were 29 recorded cases; and during this same period there were about 29,000 admissions, giving an incidence of about 1 case for every 1,000 hospital admissions. These figures probably reflect an increasing incidence as well as a better awareness of diagnosis. If the 29 cases reported during the last four-and-one-half years represent a relatively true incidence of the disease, its occurrence certainly cannot be described as rare.

Clinical Course.—The universal symptom of epiglottitis is, of course, respiratory difficulty. This is frequently abrupt in onset. The patient may seem perfectly well in the evening and awaken in the early hours of the morning with stridor and obvious respiratory distress. Classically, the stridor is inspiratory, as can be readily understood from the pathophysiology of the epiglottic swelling, but both inspiratory and expiratory stridor are noted, particularly if the larynx is involved in association with the epiglottis. Classically, also, there is no true hoarseness, inasmuch as the larynx is usually free from edema, and the characteristic sound of the voice is described as "muffled." If the patient is old enough, a frequent complaint will be sore throat and a "lump" in the back of the throat. Frequent swallowing motions will be present, and the patient may gag and vomit. A large amount of mucus is usually present in the oral pharynx. These symptoms are easily understood; the swollen epiglottis represents a mass in the posterior oral pharynx, and this elicits gagging and vomiting. Examination of the child will frequently show restlessness, stridor, use of the accessory muscles, a frightened look, and in the later stages cyanosis; in short, air hunger. Depression of the tongue in most cases will allow visualization of the greatly enlarged epiglottis. It may be useful at times to retract the tongue forward during the examination, and, uncommonly, it may be necessary to use the laryngoscope to visualize the epiglottis. There is usually associated redness of the posterior pharynx, but this is ordinarily mild in comparison to the epiglottis.

Figure I

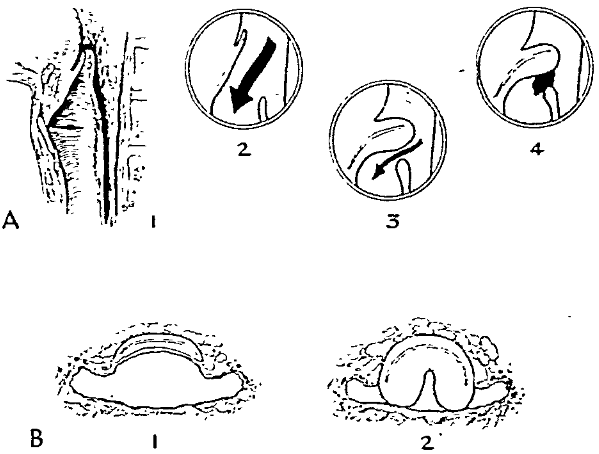

Fig. 1.—*A*, representation of mechanism of obstruction in epiglottitis: *1*, sagittal section of larynx; 2, normal airway; *3, restricted airway secondary to edematous epiglottis; 4,* complete obstruction by bolus of mucus. *B*, cross sections of epiglottis: *1*, normal epiglottis; 2, "horseshoe" appearance of edematous epiglottis.

As was stated, the onset and course of the disease are frequently rapid, as illustrated by the first patient presented, an 18-month-old child who appeared perfectly well during the day, vomited at 10 p. m., and at 1:30 a. m. was noted to have respiratory difficulty. The patient was dead at 3:20 a. m. From the time respiratory distress was first noted until the time of death, one hour and 50 minutes had elapsed. In other instances, the course is more prolonged. The average time between the onset of the first symptoms, not necessarily respiratory, and the time of admission in this series was 15 hours. In patients who did not need tracheotomies, the average time was 16 hours; in those who needed tracheotomies, it was 13 hours. The mean time of performance of tracheotomy after hospital admission was almost three hours. These figures are somewhat misleading, however, in that they are means and are brought to higher levels by a relatively few cases with a prolonged course of development. In many instances the disease progressed from the first symptom to hospital admission over the course of four to six hours, and in many instances tracheotomy was necessary immediately or at least within one to two hours. The duration of illness prior to hospitalization did not seem to vary between the various age groups, but a tendency was noted for the younger age groups to need earlier tracheotomy after admission.

The average hospital stay for patients without tracheotomy was three and one-half days and for patients with tracheotomy was five and one-half days. The tracheotomy tube was removed, on the average, four days after its placement. This longer period of hospitalization for patients with tracheotomies is readily explicable on the basis of (1) more severe disease and (2) the mechanics of tracheotomy care. Of the 35 treated cases, 12 patients received tracheotomies (34%).

Most patients came to hospital with fever (102 to 103 F [38.9 to 39.4 C]) and leukocytosis (15,000 to 20,000 white blood cells per cubic millimeter). The severity of the disease could not be correlated with the degree of leukocytosis (which ranged from 6,150 to 36,650 white blood cells per cubic millimeter) nor with the admission temperature (which ranged from 99.6 to 105.0 F [37.5 to 40.6 C]). This is in agreement with Sinclair's [1] original observation.

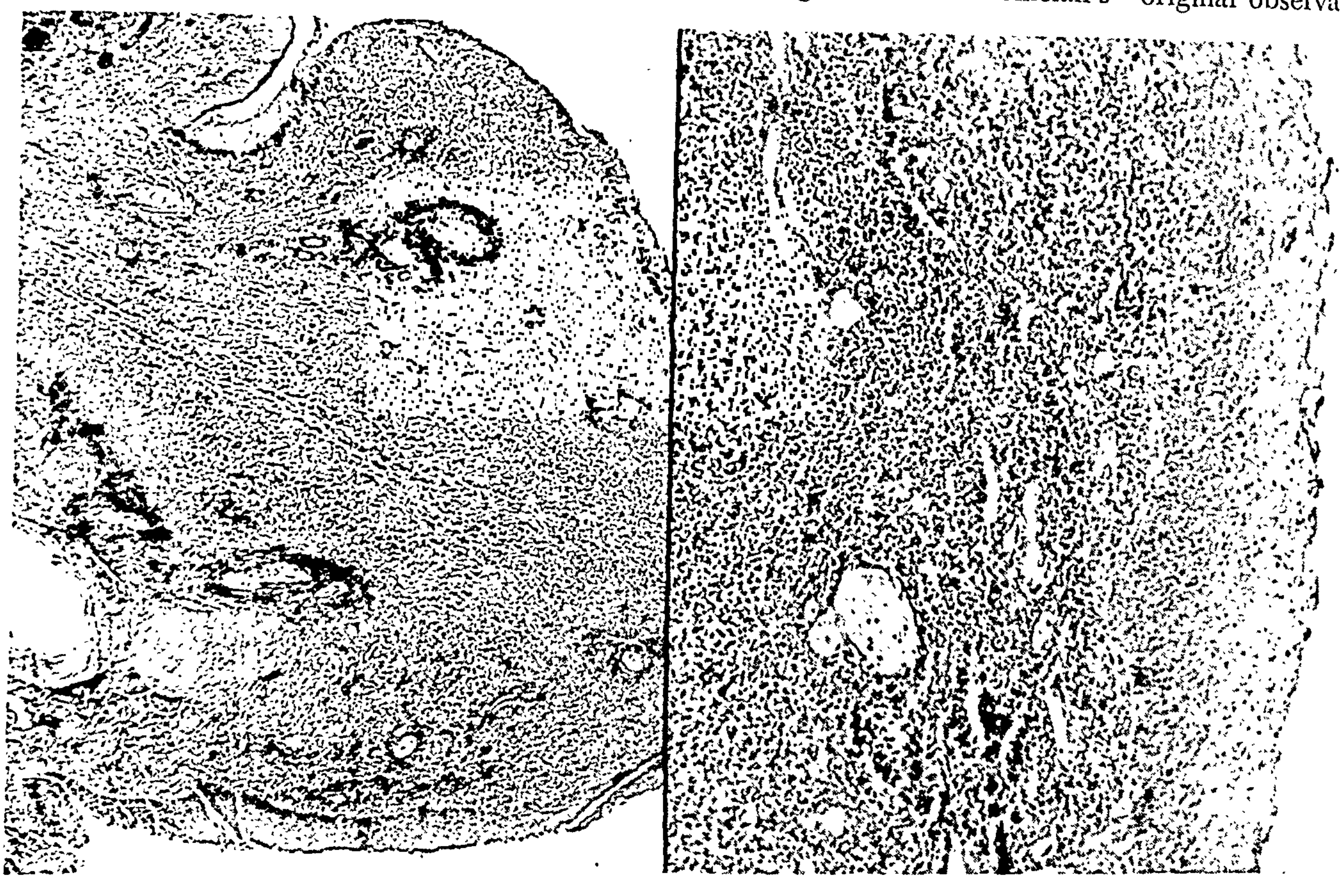

Fig. 2 (case 1).—*Left,* sagittal section of epiglottis, showing marked edema and inflammation. Epiglottic cartilage is seen at lower left-hand corner (× 22). *Right,* higher power view showing polymorphonuclear infiltration (× 127.5).

Bacteriological Investigation and Therapy

Sinclair [1] reported his 10 cases of epiglottitis as an entity secondary to Hemophilus influenzae B infection. All 10 patients had blood cultures positive for H. influenzae B. Similarly, Miller [2] (8 cases), Alexander and others [3] (10 cases), Davis [4] (3 cases), DeNavasquez [5] (1 case), and DuBois and Aldrich [6] (4 cases) all reported 100% positive cultures for H. influenzae B, either from the blood or from the epiglottis. More recently, it has become recognized that a similar clinical picture could be produced by infection with bacteria other than H. influenzae B.[7] In this series of patients, of 30 epiglottic cultures made only 2 showed predominant infection with H. influenzae B. An additional four patients showed H. influenzae B with other organisms, but Hemophilus was not predominant. Nine cases showed the combination of alpha hemolytic streptococci and Neisseria catarrhalis, four of these in addition showing staphylococci. Most patients in this series showed mixed cultures with two or three of the following organisms: streptococci, staphylococci, pneumococci, N. catarrhalis, and diphtheroids.

Only two patients of this series had blood cultures made during life. Both of these cultures were positive for H. influenzae B, and neither of the corresponding epiglottic cultures showed this organism. Both Alexander and Ellis[3] and Jones and Camps[8] have pointed out that routine epiglottic cultures will infrequently show H. influenzae B. It appears likely that the etiological agent in the cases reviewed here was more frequently H. influenzae B than the bacterial reports of epiglottic cultures would indicate. It should be stated, however, that there was no apparent difference in the clinical picture in those patients who were shown to have H. influenzae B as the etiological agent. Of the two patients with positive blood cultures, both recovered, being discharged on the fifth and third day.

Therapy.—Virtually all patients were treated with a form of humidity and oxygen therapy, most with a pediatric high-humidity oxygen tent. Table 1 shows the therapy used in 35 patients. The patients are divided chronologically in groups of 10, except for the last group of 7, and a tendency is noted toward increased use of chloramphenicol, penicillin, and steroids, in addition to the high-humidity oxygen tent, as standard therapy. Also shown in table 1 is the number of patients in each group who received a tracheotomy and the number of patients on therapy with steroids who received tracheotomies. It cannot be said, from the small sample presented here, that the use of steroids has diminished the need for tracheotomy.

Table 1.—*Specific Therapy**—*Thirty-Five Cases of Epiglottitis*

Treatment	1st 10 Patients, to March, 1955	2nd 10 Patients, to March, 1957	3rd 10 Patients, to Sept., 1958	Last 7 Patients, to July, 1959
Chloramphenicol	2	6	6	7
Penicillin	2	3	2	5
Steroids	0	4	5	4
Streptomycin	3	4	1	1
Tetracycline	1	2	1	...
Sulfonamides	2	2	1	...
Chlortetracycline	3	...	...	...
Oxytetracycline	1	...	...	...
Diphenhydramine Hydrochloride	1	...	...	...
Syrup of ipecac	1	...	...	...
Tracheotomy	4	2	3	3
%	..	...	...	... 34%
Tracheotomy with steroids	0	1	1	2

* Virtually all patients received treatment with oxygen and humidity, usually with a pediatric high-humidity oxygen tent.

At present the outline of therapy generally being used is as follows: 1. It is essential that these patients be continually observed until there is no further possibility of their having respiratory obstruction. It has been pointed out that a patient who has a borderline glottic chink may be able to maintain life, but the chink may become completely obstructed by mucus at any time, resulting in respiratory death in a matter of minutes. 2. Therapeutic use of an oxygen tent with a high degree of humidity has been extremely useful in reducing epiglottic edema. If the patient has had a tracheotomy, the high humidity is routine to prevent tracheal drying and inspissation of mucus. 3. Chloramphenicol is used because of the possibility of the H. influenzae B infection, and penicillin is used because of the frequency of alpha hemolytic streptococcus cultures. These should be given parenterally in order to achieve a rapid blood level. 4. Although there is no indisputable evidence that steroids are helpful, they should be used because of their anti-inflammatory action. Over a short course, the use of steroids is relatively innocuous.

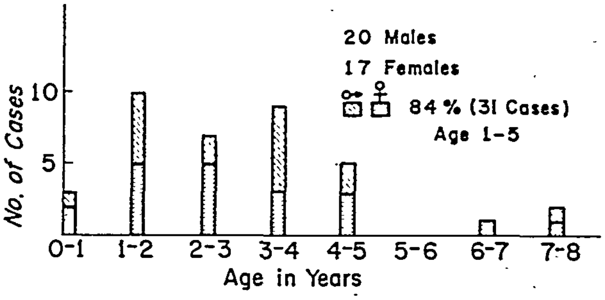

Fig. 3.—Age and sex distribution in 37 patients with epiglottitis.

5. The most important aspect of therapy is the maintenance of an airway. This will frequently demand tracheotomy for mechanical relief of the obstruction. Certainly, any patient who shows any degree of cyanosis should have immediate tracheotomy. It is not unusual to recognize significant cyanosis in retrospect, i. e., after the patient has had tracheotomy and has shown improved color. A sensible policy is to perform immediate tracheotomy on patients with cyanosis. In those who do not have cyanosis, the other modes of therapy are begun, and the patients are observed continuously for one to two hours. If improvement occurs, continued close observation is justified. If there is no significant improvement, or if deterioration occurs, tracheotomy is performed. 6. While this cannot be classified under the heading of therapy, it would seem that on the basis of the probably misleading bacteriological study in this series, routine blood cultures should be performed, in addition to epiglottic cultures, as soon after admission as is practical. 7. If a patient with cyanosis is seen in the home, the physician should stay with the patient until hospital facilities are available. If complete airway obstruction occurs, placement of a large intravenous needle (13-or-15-gauge) into the trachea or sublaryngeal area will probably maintain a life-sustaining airway until definitive therapy can be accomplished.

Report of Cases with Mortality

The mortality in reported series has varied. Table 2 shows a compilation of several series; as expected in the later series, the mortality of the treated patients has diminished markedly. In this series three patients died, two of whom were dead on admission. The three deaths are briefly reviewed below.

Case 1.—An 18-month-old girl awakened at 10 p. m. and vomited. She then went back to sleep and awakened again at 1:30 a. m., with respiratory distress. Humidification with a tea kettle was tried, but this did not provide relief. At 2:30 a. m. a physician saw the patient, and at that time respiratory stridor was noted, but no cyanosis was evident. The patient was sent immediately to the hospital. The patient arrived at the hospital at 3:20 a. m. and died promptly in the emergency room. At autopsy, the larynx was normal, but the epiglottis was markedly enlarged, the edges approximating each other. Sections of the epiglottis (fig. 2) showed intense inflammation and edema. A culture taken at autopsy was overgrown with Pseudomonas aeruginosa.

Table 2.—*Mortality in Patients with Epiglottitis*

Series	Year	Cases	All Deaths	Mortality, %
Sinclair[1]	1941	10	4	40
Alexander and others[3]	1942	10	2	20
DeNavasquez[5]	1942	1	1	100
DuBois and Aldrich[6]	1943	4	0	0
Davis[4]	1947	3	0	0
Miller[2]	1948	8	0	0
Berenberg and Kevy[7]	1958	42	3	7
Present	1959	37	3	8
Totals		115	13	11

Case 2.—A 27-month-old boy was noted to be irritable 12 hours to the time of admission and 3 hours before admission was noted to have respiratory difficulty. He was admitted to the hospital and given therapy with humidification, oxygen, and antibiotics. His condition seemed to be improving, but after a few hours he abruptly developed respiratory obstruction. An emergency tracheotomy was performed just prior to, or actually during, death. Epiglottic cultures on admission revealed a few H. influenzae B organisms and many alpha hemolytic streptococci. At autopsy, many H. influenzae B organisms were found in both lungs in association with alpha hemolytic streptococci. The anatomic findings were (1) epiglottitis, (2) laryngotracheal bronchitis, (3) pneumonitis, and (4) atelectasis of the upper part of the right lung. While it is obvious that this patient's disease was not a simple epiglottitis, the immediate cause of death was probably respiratory obstruction secondary to the epiglottic swelling.

Case 3.—A 45-month-old girl, in whom the exact onset of the disease was not well recorded, was seen in the morning by a physician, who noted some respiratory difficulty and slight cyanosis. The child was sent immediately to the hospital but on the way had a convulsion, and respiration ceased. No autopsy was performed.

Comment.—The common feature of all three of these patients was a rapid and abrupt onset of respiratory obstruction. Mechanical relief of respiratory obstruction would probably have saved all three patients.

Summary

In 37 cases of acute epiglottitis in patients admitted to a children's hospital over a nine-year period there was (1) no significant sex difference; (2) a moderate seasonal predominance (spring and early summer); (3) occurrence chiefly in preschool groups, 84% of the patients being between the ages of 1 and 5 years; (4) tracheotomy required in 34% of the patients; (5) mortality of 8%; three deaths, two in patients who were dead on arrival; and (6) bacteriological evidence of a low incidence of Hemophilus influenzae B as the offending organism, implying that epiglottic cultures only are not reliable and that blood cultures should be obtained routinely on admission.

The course and onset of epiglottitis are abrupt; in many instances it proceeds from a first symptom to severe respiratory obstruction in four to six hours. Obstruction of the airway is secondary to the marked edema of the epiglottis, which diminishes the glottic chink. A bolus of mucus impacted in the narrowed chink may cause complete respiratory obstruction. Management consists of constant observation, the use of oxygen and humidification, administration of specific antibiotics and steroids, and early tracheotomy as indicated.

Dr. S. Allison Creighton of the Pathology Department of the Children's Orthopedic Hospital gave permission to use the reproduced tissue section.

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SODIUM CONTENT OF ANTACIDS

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Two patients became edematous and their conditions deteriorated markedly after they began to take an antacid for gastrointestinal symptoms. One, a 58-year-old woman, had a history of hepatic cirrhosis; in six days of antacid medication she accumulated 3.7 liters of edema fluid. The other was a 57-year-old man who had had repeated episodes of congestive heart failure; in seven days he accumulated over 5 liters of fluid. Both patients' conditions improved when they stopped taking the antacid. Chemical analyses showed that antacid therapy had increased the sodium intake by about 0.5 Gm. per day. Other antacids in common use were analyzed and were found, in general, to contain amounts of sodium that would be seriously detrimental to patients on the verge of edema.

In the treatment of diseases such as peptic ulcer or bleeding esophageal varices, antacids are often prescribed. Concomitant liver or heart disease may require sodium restriction because of the danger of ascites and edema. In this situation we have been amazed by the occasional sudden development of edema or ascites coincident with antacid therapy.

The suspicion that the sodium content of antacids was responsible for these events prompted this investigation. Two cases illustrating the problem are presented with the method and results of analyses of various antacids and similar preparations for their content of sodium and potassium.

Report of Cases

Case 1.—A 58-year-old woman was admitted to the University of California Medical Center in December, 1955, with a diagnosis of Laennec's cirrhosis. The patient had had an episode suggestive of hepatitis in her childhood, and for 5 to 10 years prior to admission she had had occasional episodes of epigastric pain, with mild anorexia. She had suffered from poor nutrition intermittently for years. Three and one-half years prior to admission she bled vigorously from esophageal varices, and at operation a liver biopsy (the specimen showing portal cirrhosis) and a splenic artery ligation were performed. She subsequently noted the appearance of spider angiomas and palmar erythema and ascites and ankle edema, while she continued to have minor episodes of bleeding. Her weight remained fairly stable at 58 to 59 kg. (128 to 130 lb.). A gastrointestinal series demonstrated esophageal varices but revealed no evidence of ulcer. Outpatient treatment consisted of a high-calorie, salt-restricted diet and occasional administration of mercurial diuretics.

On admission to the hospital she had the usual stigmata of severe chronic liver insufficiency, with ascites and edema and obvious hepatosplenomegaly (in spite of the alleged splenic artery ligation). She was treated with bed rest, a high-calorie, high-protein, 500 mg. sodium diet, mercurial diuretics, blood transfusion, and salt-poor albumin. Her weight decreased to 55.3 kg. (122 lb.), but by the 13th hospital day had stabilized at 57.7 kg. (127 lb.) At this point she was started on therapy with Trinesia (UCLA), 30 cc. four times daily, which is an aluminum hydroxide gel magnesium trisilicate mixture with carboxymethylcellulose to maintain the suspension compounded and dispensed at the UCLA pharmacy. She continued to take Trinesia for a total of six days. During this time she gained 3.7 kg. (8 lb.) to 60.9 kg. (134 lb.), with an increase in her ascites and edema and clinical deterioration despite vigorous supportive measures. After the administration of Trinesia was discontinued her weight decreased slightly, although not to previous levels, and with use of intravenously administered albumin her condition improved clinically and she was discharged to outpatient care on the 42nd hospital day.

Comment.—Although it is presumptuous to isolate one of several variables to account for a change in her status, the patient's condition after 13 hospital days seemed stable, showing gradual improvement. With the introduction of therapy with Trinesia, containing 123 mg. of sodium per 30 cc., her sodium intake was increased by 492 mg. per day. She quickly gained weight and her condition began to deteriorate clinically, with slow reversal of this downward trend after the administration of Trinesia was discontinued. A causal relationship seems likely.

Case 2.—The patient was a 57-year-old man with a six-year history of coronary artery disease, with repeated episodes of congestive failure. He also had a duodenal ulcer, which was demonstrated by roentgenogram. He was first admitted in April, 1957,

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for seven weeks because of an acute anterior myocardial infarction. His weight at the time of discharge was 58.8 kg. (130 lb.), but dropped to 54.2 kg. (119½ lb.) while he was being cared for in the outpatient clinic. His chest remained clear and his course stable until September, 1957, when he failed to remain on his diet, took increased quantities of salt, and went into congestive failure, with a weight gain of 3 kg. to 57.2 kg. (126 lb.). He was admitted to the hospital and responded well to administration of diuretics and conservative therapy. After discharge his weight remained stable at 55.5 kg. (122 lb.) for three months. At that time, with no other change in his regimen and while continuing to remain on a low-sodium diet, he was started on therapy with Trinesia 30 cc., four times per day, for recurrence of mild ulcer symptoms. Within one week his cardiopulmonary symptoms of dyspnea and orthopnea had increased markedly. He developed 3+ edema where he had been edema-free before, rales in the lungs, and gained over 5 kg. (11 lb.) to 60.9 kg. (134 lb.). The Trinesia therapy was discontinued, and during the next month his condition progressively improved. He subsequently had remissions and relapses, but none so dramatic as the one described.

Comment.—The patient's progress was followed by one house officer over a two-year period. Although the vagaries of the course of chronic congestive failure are well known and hard to predict, the coincidence described strongly suggests that the added dietary sodium contained in Trinesia precipitated congestive failure after a period of stability, and without any other change in medication or diet.

Method

The immediate problem in analysis of the gel antacids is that their high viscosity and content of particulate matter make it impossible to use the spectrophotometer without first processing them.

The antacid samples were obtained from pharmacy stock or purchased. After thorough mixing, about 25 cc. were placed in a previously weighed casserole and covered with a watch glass. The weight of the wet sample was determined by difference to the nearest 0.01 Gm. The sample was evaporated to dryness on a warm plate, then ashed in a muffle furnace for 12 hours. After cooling, the residue was ground to a fine powder, and thoroughly mixed with 15 cc. of concentrated hydrochloric acid. This was then filtered through Whatman no. 1 paper into 100-cc. volumetric flasks, each casserole being rinsed several times with deionized water until the residue was completely transferred.

On completion of filtration, the filter paper with residue was replaced in the casserole and ashed again. The ash was then dissolved in hydrochloride and filtered. All flasks were then brought to volume with deionized water. Aliquots were analyzed directly for potassium. A preliminary dilution of 1:10 was used for sodium. Further dilutions were carried out when the concentration of the cation was found too high for optimum reading on the instrument.

When tablets were analyzed, repetitive weighing revealed no significant variation in mass of tablets randomly selected, and eight tablets (the approximate equivalent of 30 cc. liquid antacid) in porcelain casseroles were dissolved in 20 cc. of deionized water. The sample was then desiccated, again dissolved in concentrated hydrochloride, and filtered. The sodium and potassium concentrations for each sample were determined in the usual manner on a Beckman model B spectrophotometer with flame attachment, with a calibration curve prepared at the time of analysis, and with use of appropriate dilutions of stock sodium standard containing 2.338 Gm. of salt diluted to one liter and potassium standard containing 1.4912 Gm. of potassium chloride diluted to one liter.

Duplicate determinations were done and the results expressed as milligrams of sodium and potassium per liter or per usual dose of antacid (see the table).

Results

The constituents of the various preparations in the table are as described by the manufacturers and in the Modern Drug Encyclopedia.[1] This information is incomplete in that the suspending agent and other substances considered inert are generally not listed, and there are few data regarding the manufacturing process and other possible sources of sodium.

One tablet of antacid usually is considered equivalent to one teaspoonful of liquid antacid. From the point of view of acid neutralization this is not necessarily true, but for purposes of comparison the values for eight tablets and 30 cc. of liquid are given.

Sodium carboxymethylcellulose is not frequently used as an antacid, although it has good acid neutralizing properties. It is frequently used as a suspending agent in liquid preparations, however, in a concentration of about 2%. Its high-sodium content is evident, and this may explain the frequent difference between liquid and tablet preparations. An equivalent amount of tablet antacid usually contains much less sodium, the exceptions being Creamalin and Gelusil.

The relatively high content of potassium in the calcium carbonate suspension prepared at the UCLA pharmacy is due to the use of potassium salts to wash out sodium during the manufacturing process. Magnesium hydroxide and citrocarbonate are included because of their reputation as antacids in some lay groups.

In general, there is wide variation among the various preparations listed. With the exception of Trevidal and Alupec, all the currently popular hydroxide gel compounds contain at least 30 mg. of sodium per ounce, and the range extends eightfold. In contrast, calcium carbonate compound suspension as prepared in the UCLA pharmacy contains only 1.8 mg. of sodium per ounce.

Comment

In prescribing antacids, one may unwittingly violate the first principle of therapeutics and do unnecessary harm to the patient. Patients hospitalized for acute ulcer symptoms often are given 1 oz. of antacid every hour during waking hours, the total daily dose approximating 500 cc., or more, if nightly doses are given. With the exception of Alupec, Trevidal, and calcium carbonate compound suspension, the increased sodium intake on this regimen ranges from 500 to 2,500 mg. per day. Even with Alupec or Trevidal the sodium administered daily would range from 180 to 270 mg. Calcium carbonate compound suspension, which is compounded and dispensed at the UCLA pharmacy, is not generally available as a commercial pharmaceutical preparation.

Comparison of Antacid Content of Various Drugs

Drug Name	Manufacturer's Description [1]	Potassium, Mg. per Liter	Sodium, Mg. per Liter	Sodium, Mg. per 30 Cc.	Potassium, Mg. per 8 Tablets	Sodium, Mg. per 8 Tablets
Aludrox	Per teaspoonful or per tablet Aluminum hydroxide gel 1 tsp. Magnesium hydroxide ¼ tsp.	15.1	1,117.0	33.0	0.53	9.5
Alupec	Per ounce Aluminum hydroxide gel U. S. P., 2 oz. (Al_2O_3 about 1.16 Gm.) Pectin 0.26 Gm. Magnesium carbonate 0.299 Gm. Saccharin, soluble 0.08 Gm. Methyl parahydroxybenzoate 0.15%	10.0	558.7	16.7	...	...
Aluminum hydroxide gel	Aluminum hydroxide gel	10.5	2,009 0	60.0	...	...
Amphogel	Aluminum hydroxide gel	8.3	1,172.0	35.0	0.38	11.0
A. M. T.	Amphogel with magnesium trisilicate 12.5% w/v per tablet Dried aluminum hydroxide gel 0.15 Gm. Magnesium trisilicate 0.25 Gm.	47.5	1,971.0	59.1	0.57	26.4
Calcium carbonate (as prepared in UCLA pharmacy)	Calcium carbonate powder per gram K—0.46 mg. Na—3.1 mg.					
Calcium carbonate compound suspension (as prepared in UCLA pharmacy)	Low-sodium calcium carbonate suspension with magnesium oxide and methyl cellulose suspending agent	34.5	61.4	1.8	...	...
Citrocarbonate	"Antacid and alkalizing . . . salt for gastric distress . . ." per gram K—17.6 mg. Na—180.7 mg.					
Creamalin	Aluminum hydroxide gel	42.8	5,523.0	165.7	0.75	192.0
Fluagel	*Aluminum hydroxide* (Al_2O_3 as aluminum hydroxide) 3.60% Sodium chloride 1.25%	95.9	8,989.0	269.7	...	...
Gelusil	Per teaspoonful or tablet Aluminum hydroxide 0.26 Gm. Magnesium trisilicate 0.488 Gm.	23.2	1,434.0	43.0	2.24	42.5
Kolantyl	Per tablet or per 10 cc. Dicyclomine hydrochloride 5 mg. Aluminum hydroxide gel 400 mg. Magnesium oxide 200 mg. Sodium lauryl sulfate 25 mg. Methylcellulose 100 mg.	19.5	1,211.0	36.3	...	...
Maalox	Magnesium and aluminum hydroxide in colloidal suspension	22 4	1,027.0	30.8	0.27	5.12
Milk of Trinesium	Per 30 cc. Magnesium trisilicate 3.9 Gm. Aluminum hydroxide 0.65 Gm.	43.9	1,247.0	37.4	...	...
Phosphaljel	Aluminum phosphate gel with sodium benzoate 0.5%	30.0	2,733.0	72.0	...	...
Robalate	Per teaspoonful or tablet Dihydroxyaluminum aminoacetate 0.5 Gm.	10.8	1,744.0	52.3	...	...
Titralac	Per teaspoonful Calcium carbonate 0.70 Gm. Glycine 0.30 Gm. Per tablet Calcium carbonate 0.42 Gm. Glycine 0.18 Gm.	108.5	2,360.0	70.8	...	...
Trevidal	Per teaspoonful Aluminum hydroxide 90 mg. Calcium carbonate 105 mg. Magnesium trisilicate 150 mg. Magnesium carbonate 60 mg. Regonal (special vegetable gum) 35 mg. Egraine (binder from oat flour) 45 mg.	47.5	397.1	11.9	...	...
Tricreamalate	Aluminum hydroxide gel and magnesium trisilicate	2,614.0	8,227.0	246.9	...	...
Trisogel	Per ounce Magnesium trisilicate 5.2 Gm. Aluminum hydroxide 0.78 Gm.	43.9	4,591.0	137.7	...	...
Milk of Magnesia	Magnesium hydroxide	5.9	139.9	4.2	...	...
Carboxymethylcellulose powder	Per gram of powder Na—74 mg. K—0.247 mg. (1,480 mg. Na/Liter of 2% solution)					

Aluminum hydroxide gel may be prepared by a number of methods. The products vary widely in viscosity and particle size, and hence in the rate of solution in acids. It is known that such factors as the degree of supersaturation with respect to aluminum hydroxide, the pH during precipitation, the temperature, and the nature and concentration of by-product ions present are important in determining the physical, and to an extent, the chemical properties of the aluminum hydroxide.[2]

While details of the manufacturing processes are not disclosed, one manufacturer adds aluminum chloride to a solution containing sodium carbonate and sodium bicarbonate. The product of this reaction is mixed with the precipitate obtained by combining solutions of aluminum chloride and ammonia. The mixed magma is dialyzed in canvas bags, the product is mixed with some gycerin, sodium benzoate is added, and the mixture passed through a colloid mill.[2] This product is available under its official name, aluminum hydroxide gel, and under several trade names. Some commercial preparations contain more aluminum hydroxide than the official product. Sodium carboxymethylcellulose is commonly used as a suspending and emulsifying agent and in 2% solution would supply 1.480 Gm. of sodium per liter. This obviously could account for a large part of the sodium in some of the preparations, and the difference between liquid and tablet preparations may be explained on this basis.

Summary and Conclusions

One patient had Laennec's cirrhosis and bleeding esophageal varices and another congestive heart failure and a duodenal ulcer. In both patients a sudden deterioration, with accumulation of edema fluid, was associated with the administration of antacids.

There is a method for measuring the sodium and potassium content of antacids. The results from use of this method of measurement show that th currently popular antacids contain between 11. to 269.7 mg. of sodium per ounce. The source o sodium is not always known, but may be due in part to the use of sodium carboxymethylcellulose as an emulsifying and suspending agent and the use of sodium compounds in the production of aluminum hydroxide or in the sodium compounds used as preservatives. An effective, palatable, nonconstipating calcium carbonate-magnesium-oxide suspension with negligible amounts of sodium can be prepared.

Addendum

Since completion of this study, Bleifer and associates[3] reported on the sodium content of four antacids, using a different technique of measurement. The results are comparable to ours, and it was also demonstrated that the antacid sodium was absorbed and resulted in increased urinary excretion of sodium in normal persons.

The preparation of this contribution would have been impossible without the assistance of Mr. Jack Heard, Chief Pharmacist, and Mr. Joseph Beckerman, Assistant Chief Pharmacist, University of California Medical Center. In addition to supplying cogent advice and technical information, they are responsible for the preparation of the low-sodium calcium carbonate compound suspension. Mr. Gail Seright served as technical assistant.

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VARYING ATTITUDES TOWARD DISEASE.—Wounds may heal and infections run their course without any intervention by a physician, but this does not make such processes any less disease experiences. A person suffering a loss is not expected to consult a physician for the diagnosis and treatment of the ensuing grief. If the physician is to consider him as a patient, convention dictates that the patient present with a "legitimate" complaint, e. g., a physical symptom. Indeed, this is what usually happens. The grieving patient brings a physical complaint and the physician may never even learn of the bereavement. If he does, he may regard it as "natural" and irrelevant, or "noncontributory," ignoring the fact that the basis for this judgment was neither examined nor established. Many other types of examples could be given. What I wish to emphasize is that many phenomena of everyday life which are considered natural are not customarily regarded in terms of disease, even though they involve processes which basically do not differ from those which are involved in disease. The term "pathological" is a relative one, and one which is set by convention—medical, scientific, and even social. And such conventions change so that what may be considered as illness or disease at one time, or by one person, may not have been so considered at another time, or by another person. Epilepsy, drug addiction, and psychosis are examples of disease processes which have been variously regarded at different times and by different people.—G. L. Engel, M.D., A Unified Concept of Health and Disease, *IRE Transactions on Medical Electronics*, January, 1960.

SEVERE CARBON DIOXIDE INTOXICATION

TREATMENT WITH ORGANIC BUFFER (TRIHYDROXYMETHYLAMINOMETHANE)

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Recently, the occurrence of severe neurological and circulatory disorders in patients with impaired alveolar ventilation and carbon dioxide retention has been emphasized.[1] Persons with chronic lung disease are characteristically prone to develop such complications when their ventilation is further impaired by bronchial infection, bronchospasm, lung collapse, or chest surgery. Congestive heart failure, sedation resulting in respiratory depression, and elimination of the hypoxic stimulus with improper oxygen therapy are also known to be precipitating factors of carbon dioxide narcosis. If this condition is not recognized early and aggressively treated, the patient progresses from mental confusion into coma, respiratory depression, circulatory failure, and even death. The appropriate use of mechanical respirators, bronchoscopic drainage, bronchodilators, respiratory stimulants, expectorants, oxygen, steroids, antibiotics, and anticongestive failure therapy sometimes is lifesaving. In spite of this vigorous treatment, however, an occasional patient is seen too late in the course of the illness or does not respond to adequate therapy and death ensues. Moreover, acute respiratory acidosis may develop without the background of chronic pulmonary disease, for example in poliomyelitis and other neuromuscular disorders, and immediate correction of this state becomes imperative.

Administration of salicylates and acetazolamide (Diamox) has been suggested for treatment of respiratory acidosis, but results have been inconsistent and certainly not promising.[2] Infusions of sodium bicarbonate and sodium lactate have been used in the past.[3] The main difficulty encountered in attempting to buffer the acidotic blood with weak alkaline solutions is that large infusions have to be given and maintained over a long period to obtain a sustained effect.

Recently the organic carbon dioxide buffer trihydroxymethylaminomethane (THAM, TRIS) has been reported capable of preventing hypercapnia in dogs subjected to apneic oxygenation.[4] In order to evaluate the efficacy of THAM in respiratory acidosis, infusions of this substance were given to three patients with chronic pulmonary insufficiency and acute carbon dioxide intoxication.

Trihydroxymethylaminomethane is described as an organic carbon dioxide buffer because an aqueous solution of it can maintain a virtually constant partial pressure of carbon dioxide in a gas phase in contact with the solution. Administered to hypercapnic and acidotic dogs it elevated the pH and decreased the pCO_2 of the serum while increasing the total serum carbon dioxide content. Administered to three dyspneic, cyanotic, and stuporous or comatose patients, it aided in correcting the respiratory acidosis and hypercapnia in two patients, and in these the relief was followed by complete clinical recovery. In the third patient the dosage used was ineffectual but free from demonstrable side-effects. These results can be explained by the assumption that trihydroxymethylaminomethane in vivo, as in vitro, reduces the pCO_2 of arterial blood and so reduces the severity of symptoms in patients with persistent hypercapnia.

Material and Methods

Infusions of THAM were given to three patients, whose case histories are presented in the following section. The substance was administered intravenously as a solution of 0.33 M in 0.2% sodium chloride (pH of 10.38), at the rate of 300 ml. per hour. The infusion time varied in the different experiments from one to three hours. Blood samples were collected at regular intervals through an indwelling arterial needle for gas, pH, and electrolyte determination. Blood oxygen content and saturation were measured by the photometric method of Hickam and Frayser.[5] Blood carbon dioxide was determined by the method of Peters and Van Slyke.[6] The pH of whole blood was measured with a Cambridge model R pH meter glass electrode; measurements were corrected to 37 C (98.6 F) by means of Rosenthal's factor.[7] Plasma carbon dioxide content was calculated from the blood carbon dioxide content, pH, and hemoglobin level with use of the line chart of Van Slyke and Sendroy.[8] Carbon dioxide tension was calculated from these values, by means of the

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Henderson-Hasselbalch equation. All determinations were made in duplicate. Hourly urine collections were obtained through an indwelling catheter before, during, and after infusion for determination of volume, pH, and electrolyte concentration. The pH of these samples was measured as described for the blood samples. Serum and urine sodium and potassium concentrations were measured on a standard Perkin Elmer flame photometer. Serum and urine chloride concentrations were measured by the Volhard titration method. The clinical course of the patient was correlated with these determinations.

Report of Cases

Case 1.—A 51-year-old man was admitted to the hospital on April 2, 1959, with a long history of chronic bronchitis, obstructive pulmonary emphysema, and recurrent acute respiratory infections. Five years prior to admission he had developed symptoms and signs of right-sided congestive failure, and since that time he continued as a respiratory cripple with dyspnea at rest and frequent episodes of edema requiring diuretic therapy. Several days before admission he had had an upper respiratory infection, after which he became cyanotic and restless. On the day of admission, he had received an intramuscularly given sedative of undetermined type from his local physician. Shortly thereafter he became unresponsive and deeply cyanotic.

Deep cyanosis, marked respiratory distress, coma, and shock were the predominant findings when the patient reached the hospital. His temperature was 37 C (98.6 F), with blood pressure of 60/0 mm. Hg, pulse rate of 140 per minute, and respiratory rate of 50 per minute. The anteroposterior diameter of the chest was increased; breath sounds were decreased throughout; wheezes and fine inspiratory and expiratory rales were heard throughout both lung fields. The heart was enlarged, with a loud ventricular gallop. The abdomen was distended and there was a question of flank dulness. There was 2+ pitting edema of the ankles and pretibial regions. The hemoglobin concentration was 15 Gm.%, white blood cell count 35,400 per cubic millimeter, with 93% polymorphonuclear leukocytes. Results of urinalysis showed 1+ proteinuria and a pH of 5.1. Serum electrolytes were within normal limits except for low chloride levels. Blood urea nitrogen levels ranged from 78 to 30 mg.%. Mixed bacterial flora was noted on a gram stain of the patient's sputum, and cultures grew Escherichia coli. Sinus tachycardia and right-axis deviation were observed on the electrocardiogram. The chest roentgenogram showed a grossly enlarged heart and bilateral increase in bronchovascular markings.

A tracheotomy was performed on admission, and the patient was placed on a Jefferson respirator and given 100% oxygen. Shortly thereafter his arterial oxygen saturation was 97%; pH, 7.213; and pCO_2, 105.0 mm. Hg. Antibiotics, a digitalis preparation, diuretics, levarterenol, and steroids were administered. The patient's blood pressure improved after several hours, but the blood-gas findings of respiratory acidosis remained stationary for several days. On April 10, 11, and 14, infusions of THAM were given (table and figure 1). The arterial pH in-

Electrolyte, pH, and Blood Gas Findings in Patients with Carbon Dioxide Intoxication Treated by Infusions of THAM

			Specimen												
			Arterial Blood						Urine						
							Serum Electrolytes, mEq. per Liter					mEq. per Liter			
Cases, No.	Date, April 1959	Therapy	Oxygen Saturation, %	pH	Serum Carbon Dioxide Vol. 1%	pCO_2 Mm. Hg	Sodium	Potassium	Chloride	Vol. Ml./Hr.	pH	Sodium	Potassium	Chloride	Clinical Condition
1	5		97	7.213	96.4	105.0	...	...	...	...	5.100	...	...	...	Coma, shock, cyanosis†
	6		100	7.192	117.2	133.7	...	...	...	...	...	...	...	...	Semicoma
	8		98	7.274	106.6	101.4	...	...	...	...	...	...	...	...	Semicoma
	10	THAM administration													
		Before	100	7.310	101.9	90.1	143	4.0	83.7	2	8.444	...	...	...	
		During	100	7.336	105.3	88.0	...	...	...	150	7.463	...	...	...	Semicoma
		After*	100	7.427	111.9	76.6	138	4.1	82.7	...	...	...	...	...	
	11	THAM administration													
		Before	...	7.243	109.7	112.1	143	4.2	76.6	75	7.054	...	...	...	
		During	...	7.318	119.9	97.6	...	...	...	...	...	...	...	...	Stupor
		After*	...	7.306	119.9	107.4	142	5.4	76.6	180	7.454	...	...	...	
	14	THAM administration													
		Before	100	7.306	118.9	106.0	142	3.7	77.0	85	7.387	102.9	58.9	13.8	
		During	98	7.391	129.3	95.8	138	5.0	76.5	200	7.590	49.8	45.7	17.1	Stupor
		After*	99	7.393	125.8	92.9	136	4.8	75.5	20	7.644	39.0	43.0	16.2	
	20		82	7.467	83.3	52.2	...	...	...	...	...	...	...	...	Off of respirator, sensorium clear
	21		93	7.460	77.0	49.0	...	...	...	...	...	...	...	...	2 days before discharge
2	25	*On admission*	72	7.106	...	...	...	...	...	...	...	...	...	...	Stupor, cyanosis‡
		4 hr. later	...	6.974	67.96	121.17	...	...	...	...	...	...	...	...	
		8 hr. later													Sensorium clearer
		THAM administration													
		Before	19	7.137	77.8	85.6	...	...	...	83	4.955	62.3	29.7	18.8	
		During	91	7.295	82.8	75.7	139	4.6	84.0	78	5.850	25.3	23.8	5.3	
		After*	93	7.155	69.8	86.0	138	4.5	84.0	78	6.105	3.6	4.9	45.4	

* 1 hour after infusion of THAM was stopped.
† Tracheostomy was performed; patient was placed on Jefferson respirator, with 100% oxygen.
‡ Tracheostomy was performed; 100% oxygen administered per catheter; 4 hr. later Seeler respirator was used with 100% oxygen.

creased by 0.1 units, and the pCO_2 decreased by 14 mm. Hg on each occasion. During this period the patient became more responsive, although he remained stuporous. On April 15 his sensorium was noted to be clearer and his respiration less labored. From that day he was gradually weaned from the respirator, his condition continued to improve, he became fully oriented, and within a few days he was ambulatory. The next week he was discharged from the hospital in satisfactory condition, and his arterial blood oxygen saturation was 93%; pH, 7.460; and pCO_2, 49.0 mm. Hg.

Case 2.—A 61-year-old man was admitted to the hospital April 25, 1959, in acute and severe cardiorespiratory failure. He had an eight-year history of respiratory distress related to chronic bronchitis and obstructive emphysema. More recently there had been symptoms of heart failure.

The patient, in marked respiratory distress, was obese, cyanotic, and stuporous. His temperature was 38.5 C (101.3 F), blood pressure 140/90 mm. Hg, with a 15 mm. Hg paradox. The chest was emphysematous, with inspiratory and expiratory rales and rhonchi. The cardiovascular system was unremarkable, except for sinus tachycardia. The liver was felt 4 fingerbreadths below the costal margin, and there was pitting edema of the lower extremities.

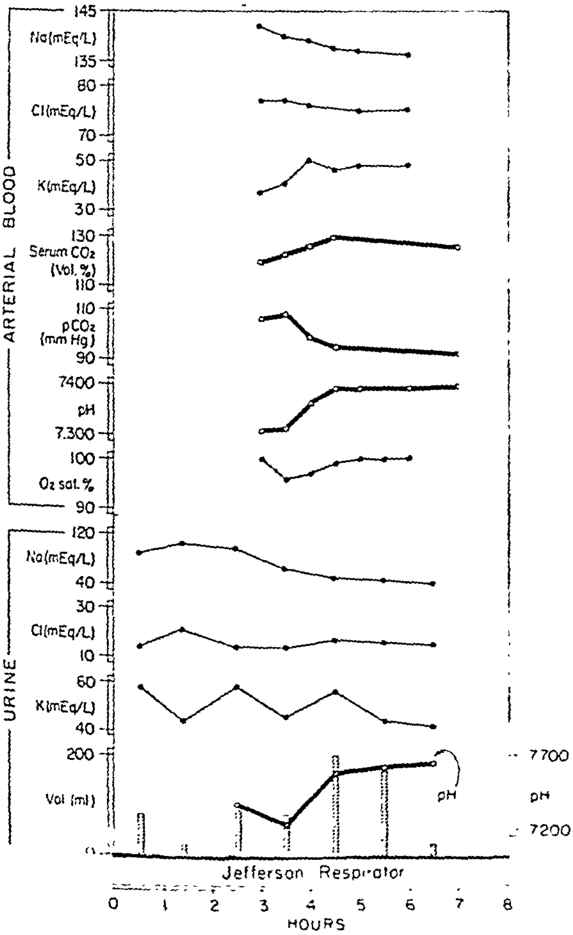

Fig. 1 (case 1).—Blood and urine pH, electrolytes, and CO_2 values before, during, and after infusion of THAM.

The hematocrit reading was 52%; the white blood cell count ranged from 7,200 to 16,520 per cubic millimeter, with 87% polymorphonuclear leukocytes. The serum electrolyte levels were within normal limits. The blood urea nitrogen level ranged from 53 to 43 mg.%. The chest roentgenogram showed bilateral pulmonary fibrosis and emphysema, with a number of large cysts on the right, and cardiac shadow grossly enlarged. Frequent ventricular extrasystoles and an incomplete right bundle-branch block were shown on the electrocardiogram.

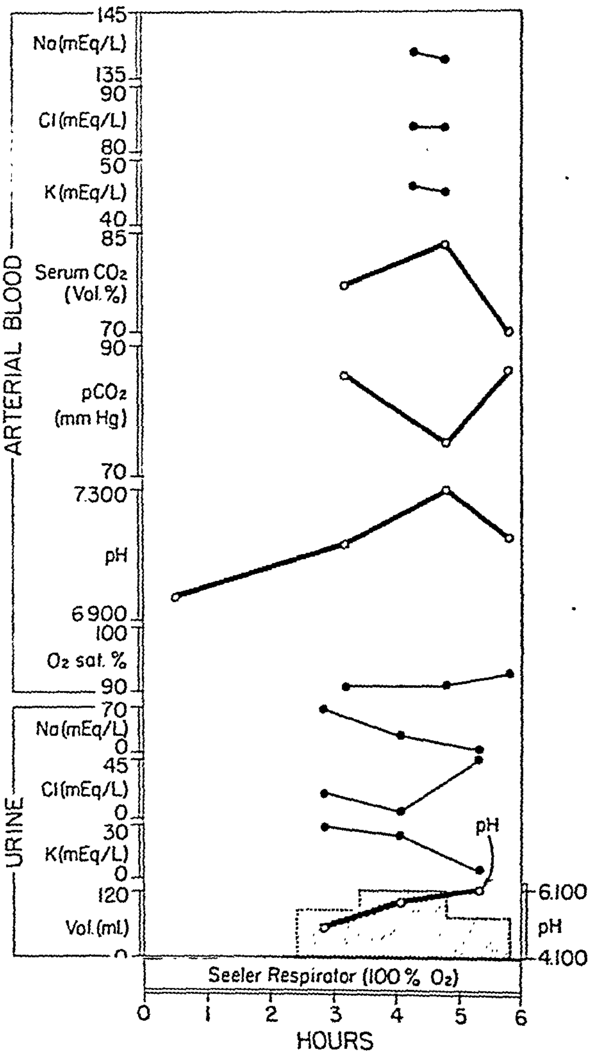

Fig. 2 (case 2).—Effect of infusion of THAM on blood and urine modalities.

Routine supportive measures, along with antibiotic and intensive anticongestive failure treatment, failed to improve the patient's cardiorespiratory difficulties. His arterial oxygen saturation was found to be 72%, and his arterial pH 7.106. A tracheotomy was then performed, but the arterial blood pH decreased to 6.974, and the pCO_2 was 121.1 mm. Hg. Thereafter ventilation was con-

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tinually assisted by way of an automatic positive-negative respirator (Seeler). After three hours the arterial pH had increased from 6.974 to 7.137. At this time, THAM was administered during a one-hour period. As shown in the table and figure 2, the arterial pH was further raised from 7.137 to 7.295 and the pCO_2 lowered from 85.6 to 75.7 mm. Hg. After assistance with ventilation and infusion of THAM, the patient's condition improved dramatically; he became oriented, and his respiratory distress was less pronounced. The subsequent course was one of steady improvement. By the fifth day he was afebrile and able to maintain adequate ventilation without mechanical assistance. After three weeks in the hospital he was in satisfactory condition and ready for discharge.

Case 3.—A man aged 48 years was brought to the emergency room on April 16, 1959, deeply cyanotic and in coma and shock. The history obtained from his family was one of asthma of about two years' duration. This had been worse for about two weeks prior to admission and was associated with productive cough. The day of admission, while on his way to the hospital, the patient became acutely and severely short of breath and felt extremely weak. He entered the outpatient department, sat in a chair, quietly slumped over, and became unresponsive.

After emergency treatment was instituted, he remained cyanotic and comatose, but his blood pressure returned to 150/30 mm. Hg; he had a pulse rate of 130 per minute and a respiratory rate of 42 per minute. The chest showed decreased breath sounds bilaterally, with wheezes and rhonchi scattered throughout. There was sinus tachycardia and a loud ventricular gallop. Results of examination of the abdomen and extremities were unremarkable. Neurological examination was unrevealing, except that the patient was responsive only to painful stimuli.

An electrocardiogram showed no significant abnormality. An arterial blood sample obtained in the emergency room indicated a marked degree of anoxemia (oxygen saturation of 67.0%) and respiratory acidosis (pH of 6.958 and pCO_2 of 133.4 mm. Hg).

In spite of emergency therapeutic measures, including bronchial drainage by bronchoscopy and tracheotomy, his respiration became weaker and shallow. An intravenous infusion of THAM was started. About 20 minutes later respiration gradually ceased.

An autopsy was performed, which revealed mucous plugs in bronchi and bronchioles, bronchitis, bronchiolitis, emphysema, and atelectasis. There was slight hypertrophy and dilatation of the heart, with spotted myocardial scarring. Other organ systems were unremarkable.

Results

The effect of THAM infusion on arterial pH, blood gases, and electrolytes and on urine volume, pH, and electrolytes is summarized in the table. The most constant changes during infusion of THAM consisted of elevation of arterial blood and urinary pH, elevation of serum carbon dioxide content, and significant decrease of arterial blood pCO_2. All other measured parameters showed no significant or consistent change, except for the urine volume, which tended to increase during the period of THAM administration.

Immediate clinical improvement was observed with the administration of the drug in one patient, and it was believed that it was beneficial in supporting the other patient while the more conventional measures were used. One patient (case 3) was given THAM intravenously as an emergency treatment in the hope of rapidly correcting his arterial blood pH which was 6.958 on admission to the hospital. This case is not being reported in the summary chart, since the effect of the drug could not be properly evaluated due to the fact that the patient died about 20 minutes after the infusion had been begun and no follow-up samples of arterial blood gases were obtained. Clinically, no toxic effect could be demonstrated during or after the infusions of THAM.

Comment

Acute hypercapnia with acidosis in patients without previous lung disease is known to produce toxic effects at the tissue level. It is well recognized, however, that patients with chronic pulmonary diseases tolerate comparable degrees of retained carbon dioxide and compensate for the acidosis.[9] With additional embarrassment of respiration and further carbon dioxide retention, decompensation may occur and coma, shock, and death result.

Nahas[4] has shown that THAM can prevent the elevation of carbon dioxide tension to toxic levels in hypoventilated dogs.[4] Our experience with THAM in severe respiratory acidosis occurring on a background of chronic hypercapnia, although limited, indicates that small amounts of this substance will correct pH and pCO_2 within 30 to 40 minutes. One patient (case 1) showed marked improvement after infusion. The other patient (case 2), while showing partial correction of the acidosis and ultimate recovery, did not manifest immediate improvement after the infusion. It should be noted that in patients with chronic lung disease and carbon dioxide intoxication, clinical amelioration may lag four to six hours behind the blood gas changes.[1b] Although relatively small doses of intravenously given THAM will begin to correct pH and pCO_2 within a short period, a minimum of about 30 minutes is required for significant correction of the acidotic state. One of our patients (case 3) died about 20 minutes after the beginning of the infusion, when correction of acidosis probably had not yet been achieved. In this patient there was no pathological evidence of organ damage which could have been attributed to the administration of the drug.

It is our impression that THAM is a useful adjunct in correction of severe respiratory acidosis in illnesses with chronic carbon dioxide retention. It is also suggested that in situations of acute respiratory acidosis without lung disease, for example during open-heart surgery or in neuromuscular disorders such as poliomyelitis and myasthenia gravis, infusion of THAM may be lifesaving. Finally, THAM given as a prophylactic measure could be considered if respiratory acidosis is anticipated in any of the conditions mentioned above.

The buffering effect of THAM is not well understood. Organic carbon dioxide buffers are capable of maintaining a virtually constant pressure of carbon dioxide in the gas phase.[10] THAM, the organic buffer used in our experiments, is an aqueous solution with a pH of 10.38 which binds carbon dioxide reversibly, mainly according to the general equation $(R - NH + H_2O + CO_2) \rightleftharpoons (HCO_3^- + R^+NH_2)$. In vitro, any carbon dioxide formed by metabolic processes is removed by this reaction proceeding from left to right, and any carbon dioxide used is replaced by the reverse process.

It is known that chronic carbon dioxide retention leads to increase in the body stores of carbon dioxide.[11] Muscles, brain, and bones seem to be the storage organs.[12] It appears likely that whenever the blood carbon dioxide concentration is in any way rapidly lowered, the gradient between tissues and blood will increase. This will have the effect of increasing carbon dioxide concentration in the blood stream, removing it from the tissues in the acid form. Therefore, the blood carbon dioxide tension and content will depend on two factors, i. e., the amount of carbon dioxide removed from the blood by lungs and kidneys and the amount shifted from the intracellular to the extracellular fluid and blood.

Preliminary studies carried out in our laboratory on dogs made acutely hypercapnic and acidotic indicate that THAM produces in them the same effects noted in our studies on human beings, i. e., elevation of pH, decrease in pCO_2, and increase in the total serum carbon dioxide level of arterial blood.[13] Moreover, during infusion of THAM in dogs the urine bicarbonate excretion and carbon dioxide content in the expired air were increased. These findings suggest that during infusion of THAM large amounts of carbon dioxide are drawn from the saturated tissues into the blood stream. It is postulated that THAM is effective by way of the mechanism described in vitro as well as by producing a shift of carbon dioxide from tissues to blood. Only by summation of these two mechanisms can one fully explain the results obtained in our studies.

Summary

Infusions of an organic carbon dioxide buffer trihydroxymethylaminomethane (THAM) were given to three patients with chronic lung disease, superimposed infection, acute respiratory insufficiency, and carbon dioxide narcosis. In two of the patients (cases 1 and 2) infusions of THAM aided in correcting the respiratory acidosis and hypercapnia and complete clinical recovery occurred. One patient (case 3) did not respond to infusion of THAM and died. No side-effects were observed.

The mode of action of the drug is not clear, but apparently, by acting as a buffer, it increases the pH of the blood while lowering the carbon dioxide tension and increasing the total carbon dioxide content.

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The trihydroxymethylaminomethane used in this study was provided as THAM by the Sigma Chemical Co., St. Louis, Mo.

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MYOCARDIAL INFARCTION WITH BUNDLE-BRANCH BLOCK COMPLICATED BY SEPTAL PERFORATION

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A physically active man began, at the age of 69 years, to have a series of episodes of severe chest pain. At the age of 71 years an attack of intense and persistent substernal pain, unaffected by medication, caused him to enter a hospital. On the third day the return of pain was accompanied by a decline in blood pressure until neither blood pressure nor radial pulse could be obtained and dyspnea and anuria supervened. At autopsy, eight days after the onset of pain, and three and one-half days after the decline had led to the diagnosis of septal perforation, an irregularly shaped opening, measuring 1.5 cm. in diameter, was found in the interventricular septum, permitting communication between the right and left ventricles.

Perforation of the interventricular septum is a serious complication of myocardial infarction. Although the problem has been known for many years, it is only recently that the condition has been emphasized in medical literature. In a series of 133 cases of acute myocardial infarction, McQuay and colleagues [1] reported that 20 patients died from rupture of the heart, an incidence of 15%. Fourteen ruptures were of the free wall and six of the ventricular septum. Wessler and co-workers [2] reported a total of 261 histologically proved acute infarcts with 19 perforations of the heart, an incidence of 7%. Fourteen ruptures were of the free wall and five of the interventricular septum.

Accurate diagnosis of interventricular septal perforation has great prognostic significance for the clinician. This reported case has most of the features that characterize such a perforation. The patient had been observed for two years prior to the terminal illness and rather mild episodes of anginal pain at infrequent intervals had been his chief complaint. The electrocardiographic patterns are of particular interest in that they show a transient or intermittent left bundle-branch block.

Report of a Case

The patient was first seen on Oct. 18, 1956. He was an active man, aged 69 years, who had been retired for several years. He complained of precordial pain which had been present intermittently for one month. This was of short duration and might have been brought on by exertion. In August, 1951, an electrocardiogram was reported to be normal and an electrocardiogram at this time was also normal. Clinically, he gave the impression of having angina pectoris. The patient was next seen on March 11, 1957, because of severe anterior chest pain located to the right of the sternum in the third interspace. The pain had lasted for about five minutes. An electrocardiogram taken at this time is shown in figure 1, *left*. On Jan. 9, 1958, the patient was again examined because of anterior chest soreness of two days' duration and one severe five-minute episode of substernal pain. An electrocardiogram showed a left bundle-branch block (fig. 1, *right*). Consequently, he was hospitalized for 13 days. After the first two days of hospitalization, he did not complain of pain. Six months later on July 2, 1958, the electrocardiogram showed no eviden of the left bundle-branch block (fig. 2).

He had no further chest pain or cardiac symptoms until the present illness, which began Nov. 1 1958. He was then 71 years of age. The patient wa seen at home because of persistent substernal pai which began during the early morning hours. H had not obtained relief by taking nitroglyceri The pain did not radiate and he did not perspir The temperature and blood pressure were norma Lungs were clear, the heart rhythm was regula tones were muffled, and no murmur was heard. H was given 50 mg. of meperidine (Demerol) hydrochloride intramuscularly and hospitalization was advised. The patient refused to return to the hospital because he had just been discharged on the day before after 10 days of treatment for pneumonia. He was seen again on Nov. 11, 1958. Meperidine therapy had given him temporary relief from chest pain but the pain had recurred in a more severe form. Physical findings had not changed from the preceding day. On Nov. 13, substernal pain became so intense that he consented to hospitalization.

On admission his blood pressure was 140/80 mm. Hg, pulse was 94 per minute, and temperature was 100.4 F (38.0 C). The lungs were clear. There was no dyspnea, cyanosis, or edema. The heart was normal in size, rhythm was regular, tones were muffled, and no murmur was heard. Laboratory findings were reported as follows: hemoglobin 15.6 Gm. per cubic centimeter; erythrocytes 4,800,000 per cubic millimeter; and leukocytes 14,250 per cubic millimeter. There were 84 segmented leukocytes and 16 lymphocytes. Urinalysis showed a trace of albumin and a few granular casts. An electrocardiogram revealed a left bundle-branch block and evidence of a recent anterolateral myocardial infarction (fig. 3).

A portable bedside chest roentgenogram revealed a residual infiltrate in the middle of the lung field on the right. The cardiac silhouette was normal. It was believed that the patient had a myocardial infarction with recurrence of left bundle-branch block. He was given pentaerythritol (Peritrate) tetranitrate, with phenobarbital, and meperidine for relief of pain. By the morning of the second day of hospitalization the chest pain had disappeared. At noon he received 300 mg. of bishydroxycoumarin (Dicumarol). During the afternoon he had four loose stools, perspired profusely, and complained of palpitation. At 5 p. m. the blood pressure was 114/72 mm. Hg. The lungs were clear. Over the entire precordium there was a loud harsh systolic murmur transmitted to the left axilla. This was the first time a murmur was heard. It was believed that the patient had a perforation of the interventricular septum. He was placed in an oxygen tent. The next day he complained of pain across his anterior chest, made worse by deep inspiration. Blood pressure was 100/60 mm. Hg. The sedimentation rate was 30 mm. per hour; prothrombin time was 45% of normal; and the serum glutamic transaminase (S-GOT) level was 55 units. That evening he was restless and perspiring profusely. The blood pressure was 80/60 mm. Hg. On Nov. 16 the temperature had risen to 102.6 F (39.2 C). A blood pressure reading could not be obtained, the radial pulse was not felt, and he was nauseated and could not void. Later in the day he became dyspneic. A Foley catheter was inserted into the urinary bladder but no urine was obtained. On Nov. 17 the patient still remained in shock. The radial pulse was not felt and blood pressure could not be obtained. The leukocyte count had risen to 34,700 per cubic millimeter; sedimentation rate was 38 mm. per hour; the S-GOT level was over 600 units; the nonprotein nitrogen level was 146 mg. per 100 cc.; and blood urea level was 62.6 mg.%. The patient died Nov. 18, eight days after the onset of pain and three and

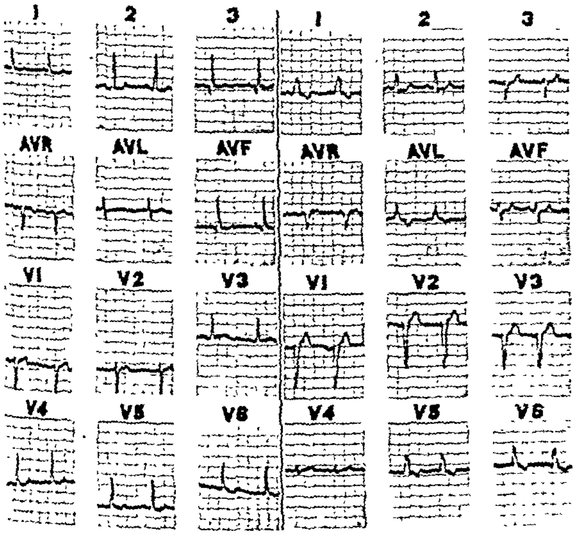

Fig. 1.—*Left,* electrocardiogram made March 11, 1957, 10 hours after attack of angina. *Right,* ECG made Jan. 9, 1958, first time left bundle-branch block was evident.

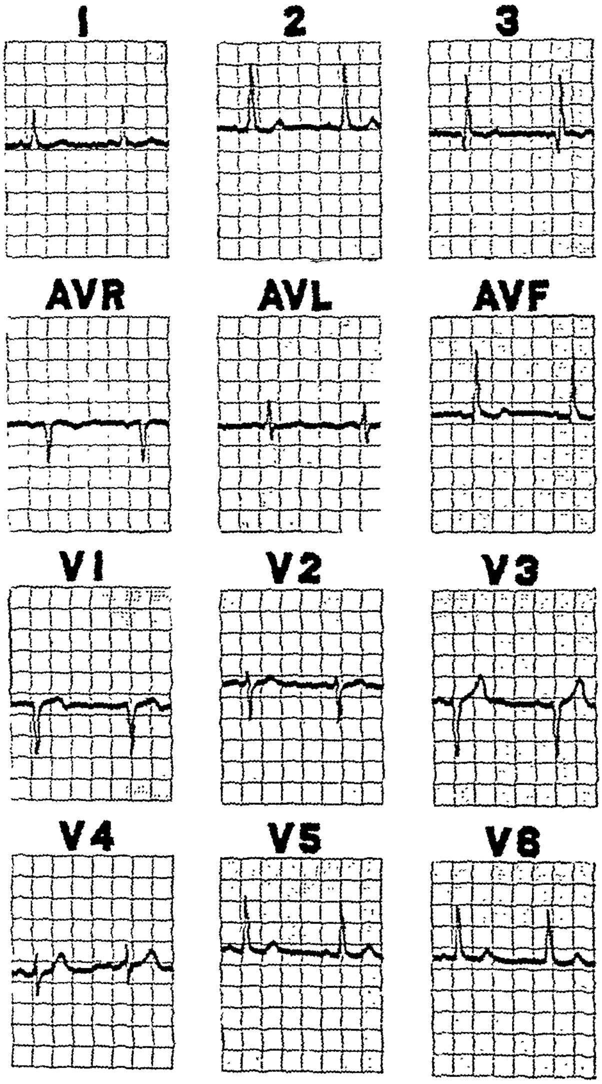

Fig. 2.—Electrocardiogram made July 2, 1958. Note disappearance of bundle-branch block.

one-half days after septal perforation was diagnosed clinically. He had been anuric for two and one-half days.

At autopsy no free fluid was found in the pericardial sac. The heart measured 12 cm. in length and 10 cm. at the base. The pericardium over the anterior and posterior aspects of the lower third of the left ventricle was dull in color. The myocardium was pale reddish gray and of decreased consistency. The lower one-third of the anterior wall of the left ventricle, the ventricular septum, and the lower one-fourth of the posterior wall of the left ventricle were yellowish gray, dry, amorphous, and soft. This tissue was sharply demarcated from the intact myocardial tissue. The ventricular wall in the affected area was thinned and measured 0.3 cm. in thickness.

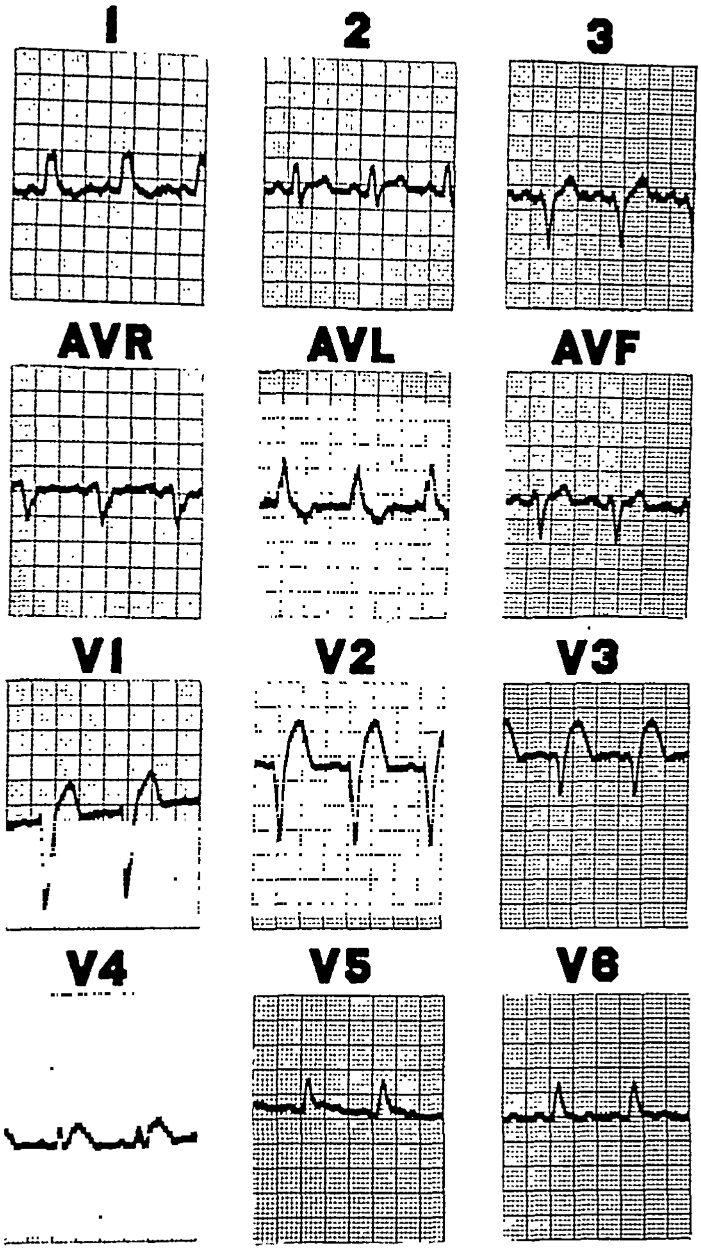

Fig. 3.—Electrocardiogram made Nov. 13, 1958, during patient's last illness. Note reappearance of left bundle-branch block with suggestion of recent anterolateral myocardial infarction.

In the ventricular septum near the apex there was an irregularly shaped opening measuring 1.5 cm. in diameter, through which the right and left ventricles communicated. The edges of the opening were covered with dark reddish gray, soft partially liquified blood clots, which were firmly adherent to the myocardium. The valves were thin and smooth. In the intima of the coronary arteries were numerous atheromatous and calcified plaques which narrowed the lumen in many areas. One such plaque was present in the anterior descending branch of the left coronary artery about 0.5 cm. below its origin. It was covered with a firmly adherent dry gray-brown blood clot which completely closed the arterial lumen. Both kidneys were normal. The urinary bladder was contracted and did not contain urine.

Comment

A person with a myocardial infarction who then suffers a perforation of the interventricular septum presents a rather characteristic clinical picture. The patient very suddenly becomes worse. This catastrophe may occur as early as a few hours after the infarction or as late as a month. Most perforations occur within the first 10 days.[3] There is often an increase in pain and sweating is profuse. Shock is evident early. Restlessness, dyspnea, cyanosis, congestive failure, and anuria frequently occur.[3c] A systolic murmur becomes audible and is heard best over the third and fourth intercostal spaces to the left of the sternum. It is usually transmitted over the entire precordium. A systolic thrill is often present. In rare cases no murmur is heard, and when this occurs it is thought to be due to a very large defect in the septum.[3b]

According to Wessler and colleagues [2] the pathological conditions common to all ruptured hearts are a fresh coronary artery occlusion; a recent myocardial infarct that is transmural; a myocardial infarct that is poorly supplied with collateral vessels; and a myocardial infarct in which fibrosis is entirely absent in at least one area. Perforation of the interventricular septum may be single or multiple and usually occurs near the apex.

Cardiac rupture may be related to exertion, because perforation is slightly more common in psychiatric patients and coroners' cases than in patients who die in a general hospital.[2] Perforation is more frequently seen in the older age group. Bond [3b] reports the average age to be 61 years. Aarseth and Lange [3a] did not find myocardial perforation in men under 50 years of age and women under 60. The condition is much more common in women than in men. Many of the patients who suffer a perforated septum have never had a previous infarction. The presence or absence of angina pectoris prior to the terminal infarction does not seem to be significant.

It has been stated that the presence of hypertension and strain are important factors in the production of rupture. The influence of anticoagulant therapy on rupture of the heart is disputed. Lange and Aarseth[3a] reported the incidence of myocardial rupture in patients who received effective anticoagulant therapy to be about twice as high as in a control group. McQuay and colleagues[1] found no significant change in the frequency of rupture when anticoagulants were given. In our patient bishydroxycoumarin was given four hours before the perforation was diagnosed clinically.

Presence of intermittent or transient bundle branch-block is unusual,[4] and rarely does one find it associated with a perforation of the interventricular septum. In figure 3, the positive displacement of the RS-T segment and a positive T wave in V_5 suggests the presence of a recent anterolateral myocardial infarction in the presence of a left bundle-branch block.[5] However, Burch and Winsor[6] state that in left bundle-branch block the initial and entire QRS complex is disturbed by the block. This makes it impossible for the pattern of infarction to manifest itself.

Prognosis after perforation of the interventricular septum is poor. Bond and colleagues reported that half of the patients survived less than one week, only five lived longer than eight weeks, and one lived five years.[3b] The treatment is essentially the same as that for uncomplicated myocardial infarction. Perhaps at some time in the future surgical repair of this defect may be feasible.[3c]

Summary

In a case of myocardial infarction complicated by a perforation of the interventricular septum, an interesting feature was the changing electrocardiographic pattern which indicated an intermittent or transient left bundle-branch block.

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TAPE-RECORDING OF HEART SOUNDS IN SCREENING CHILDREN FOR HEART DISEASE.—The recent dramatic progress in the diagnosis, treatment, and surgical correction of heart disease has stimulated renewed interest in the prevalence of cardiac problems in the school-age child. . . . An automated tape-recording unit for use in screening large populations of school children for heart disease has been developed and field tested. A technician can produce good quality apex and base heart sound recordings from 250 children during an average school day. The physician can listen to these recordings at a rate of 140 children per hour, recalling for examination each child considered to have an abnormal recording. Since almost all heart disease in children has some acoustic manifestation, a screening technic based on the heart sounds seems to be a logical one. The studies done with this unit have demonstrated its ability to select children with heart disease from a large number of normal children.—J. M. Smith, M.D., and others: Use of Tape-Recorded Heart Sounds in Screening of Children for Heart Disease, *Circulation*, November, 1959.

J.A.M.A., July 2, 1960

STAPHYLOCOCCIC ENTEROCOLITIS

REPORT OF SIX CASES WITH TWO FATALITIES AFTER INTRAVENOUS ADMINISTRATION OF N-(PYRROLIDINOMETHYL) TETRACYCLINE

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The use of N-(pyrrolidinomethyl) tetracycline, a new tetracycline suitable for intravenous injection, has been regarded as largely free from risk, especially with regard to staphylococcic enteritis. However, six patients were observed with staphylococcic enteritis after postoperative intravenous treatment with this drug. In four patients, erythromycin or spiramycin treatment was successful. A fifth patient with severe diarrhea died of staphylococcic gastroenteritis with sepsis 10 days after operation. The sixth patient died of acute necrotizing staphylococcic gastroenteritis three days after operation. The tetracycline concentration in the intestinal lumen after intravenous administration, even if 10 times lower than after oral treatment, is adequate to inhibit normal flora, thus favoring staphylococcic superinfection. Careful supervision of patients thus treated is, therefore, essential.

Sudden death due to side-effects of drugs generally considered safe is an appalling catastrophe which afflicts not only the patient and his relatives but the treating physician or surgeon as well. No effort must be spared to minimize the risk of such incidents; for this reason, side-effects not previously recognized should be reported so that future patients will receive whatever benefit may result from early and correct diagnosis and treatment.

With the recent development of N-(pyrrolidinomethyl) tetracycline, a new tetracycline derivative introduced in Germany in 1958[1] under the name Reverin, and more recently in the United States under the name Syntetrin, the well-known drawbacks of the older tetracycline preparations available for intravenous administration have been largely overcome. Without going into pharmacological detail, the main advantages of this remarkable drug may be summarized as follows: better solubility—by a factor of 10—and greater stability in solution than tetracycline hydrochloride, and excellent local and general tolerance when injected intravenously in a dose of 250 mg. in 10 ml. of solution within one or two minutes. In the experience of European clinicians,[2] one dose of 250 mg. in 24 hours will suffice for most infections; in severe cases, twice this amount is recommended. Only rarely need higher doses of 750 mg. to 1 Gm. be given.[3]

Side-effects reported so far have been few and unimportant. After intravenous injection of 250 mg. in one minute, about 70% of patients experience a "bitter" or "burning" sensation on the tongue. Some few incidents, presumably allergic in nature but as yet relatively harmless (flush, collapse and tachycardia,[2b] and urticarial dermatitis [2d]), have been encountered, but in view of the route of administration, dangerous anaphylactic reactions might presumably turn up as more cases are being treated. Recently, one instance of severe anaphylactic shock with temporary disappearance of peripheral blood pressure and cerebral ischemia with generalized convulsions was observed, starting a few minutes after the 10th intravenous injection in a series of daily treatments with N-(pyrrolidinomethyl) tetracycline. Immediate administration of epinephrine hydrochloride was followed by recovery after about one-half hour.[4]

After daily intravenous administration of 250 mg. of N-(pyrrolidinomethyl) tetracycline, stool concentrations of 5 to 10 mcg. of tetracycline per gram were found, compared to 65 to 95 mcg. per gram after a fourfold oral dose of 250 mg. of tetracycline hydrochloride,[5] which dosage schedules have been found therapeutically equivalent in human clinical cases[6] and in animal experiments.[7] On the basis of these experimental findings and early clinical experience, it has been repeatedly claimed[8] that N-(pyrrolidinomethyl) tetracycline will not appreciably derange the intestinal flora and that, therefore, its administration is attended by practically no risk of staphylococcic enterocolitis, rightly judged to be the most redoubtable complication of oral tetracycline therapy. The case histories to be presented here (part of which were reported earlier as a preliminary communication[9]) demonstrate, however, that this assumption—which at first might not seem unreasonable—is, in fact, untenable and may conceivably prove dangerous if it leads to delay in diagnosis and treatment. Some cases of diarrhea were actually observed by other authors[10] but were attributed to causes other than the antibiotic.

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Report of Cases

CASE 1.—A 56-year-old man was admitted with arterial hypocirculation of both legs, demonstrated by arteriography to stem from a subtotal obstruction of both external iliac arteries. At operation on March 6, 1959, the obstruction was bypassed on both sides with a Teflon prosthesis stretching from the common iliac to the femoral artery. Two doses per day of 250 mg. of N-(pyrrolidinomethyl) tetracycline were given intravenously for four days postoperatively. On the fourth day, the onset of severe diarrhea was accompanied by a rise in body temperature to 39.3 C (102.7 F), chills, and a fall in systolic blood pressure from 120 to 80 mm. Hg. A stool smear revealed gram-positive cocci, subsequently identified as Staphylococcus aureus resistant to penicillin, streptomycin, and the tetracyclines. Administration of N-(pyrrolidinomethyl) tetracycline was discontinued immediately, and intensive treatment with blood transfusions, infusions of saline solution, and 500 mg. of erythromycin every eight hours was begun. The general condition of the patient rapidly improved, the diarrhea stopped three days later, and the patient was discharged on March 31 after an otherwise uneventful course.

CASE 2.—In a 76-year-old man the presence of an arteriosclerotic aneurysm of the abdominal aorta was confirmed by aortography in June, 1958. The patient's relatives, however, refused operation. On March 12, 1959, the patient was readmitted in an emergency with the clinical picture of a ruptured aneurysm: abdominal pains, rapid growth of the tumor previously found, extreme pallor, and shock. Operation was immediately begun. With administration of 12.5 liters of whole blood, and with a resection under hypothermia of the bleeding aneurysm (almost as large as a man's head) and its replacement by a DeBakey bifurcation, prosthesis was accomplished by one of us (A. S.). Postoperatively, two intravenous doses of 250 mg. of N-(pyrrolidinomethyl) tetracycline were given daily. On the morning of the fourth day, a rise in temperature to 37.9 C (100.2 F) and tachycardia occurred, followed by diarrhea some hours later. Staph. aureus was cultured from the stools. Treatment with infusions, blood transfusions, and 500 mg. of erythromycin every eight hours was begun forthwith and led to cessation of the diarrhea after a few days, the general condition of the patient not having suffered severely. He left the hospital after an otherwise smooth course on April 4 and, at the latest follow-up examination on Nov. 2, was in excellent health, with normal circulation of both legs.

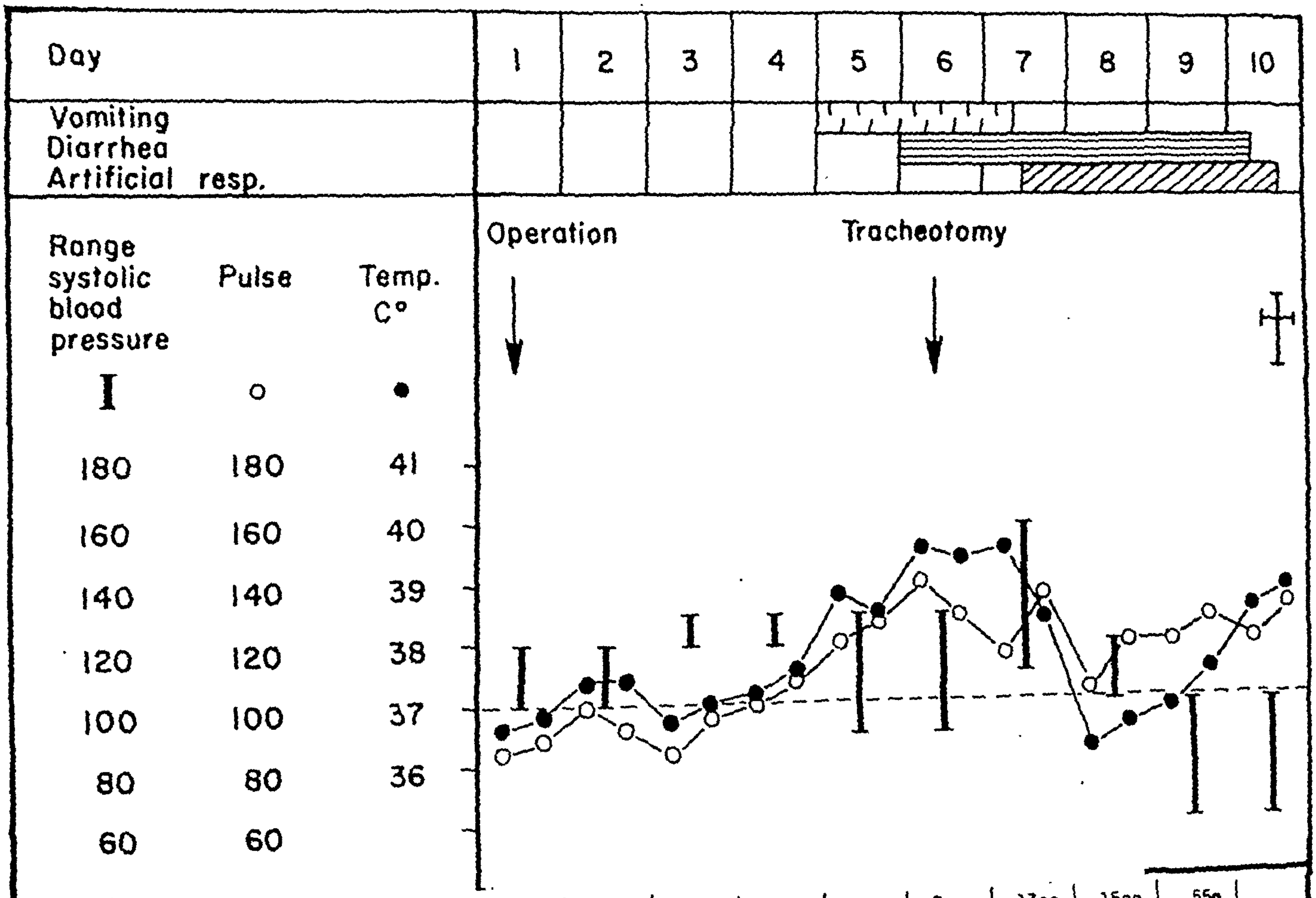
CASE 3.—A 64-year-old woman, who, during the winter of 1959, had progressive anemia with occult blood in the stools, was admitted on March 10 for examination. A barium enema examination disclosed a stenosing tumor of the transverse colon. After preoperative preparation of the bowel with phthalylsulfathiazole and (on the day before operation only) chloramphenicol, the tumor was resected and an end-to-end anastomosis performed without difficulty on March 18.

Histological examination of the specimen obtained demonstrated an adenocarcinoma without regional metastases. Postoperatively, two doses of 250 mg. of N-(pyrrolidinomethyl) tetracycline were administered intravenously from March 18 to March 22 inclusive. On the evening of March 24, the body temperature rose to 38.5 C (101.3 F) and vomiting and diarrhea set in. The stools contained gram-positive cocci. Treatment with infusions and 500 mg. of spiramycin every eight hours was instituted, therapy with the latter antibiotic being continued until March 30. The diarrhea stopped on the third day of treatment, the patient's general condition—precarious at first—improved rapidly, and she was discharged on April 1, without further complications. The report of follow-up examination on May 25, 1959, was: good health, weight increase of 8 kg. (17.6 lb.), and normal defecation.

CASE 4.—An 85-year-old woman was treated with local injections of a sclerosing solution for rectal prolapse in December, 1958. Temporary success being followed by a relapse, the patient was readmitted on May 14, 1959, and on May 20 plastic repair by means of fascial strips was performed. On May 20 and 21, two doses of 250 mg., and from May 22 to 24, inclusive, one dose of 250 mg., of N-(pyrrolidinomethyl) tetracycline were given daily. On May 25, the patient received 1 million units of penicillin and 1 Gm. of streptomycin intramuscularly. On May 26, vomiting and diarrhea commenced, accompanied by general deterioration in the patient's condition but without fever or shock. The stools contained gram-positive cocci, subsequently identified as Staph. aureus resistant to penicillin, streptomycin, and the tetracyclines. Treatment with infusions, blood transfusions, and 500 mg. of spiramycin every eight hours eliminated the diarrhea after three days and effected a rapid general improvement. The patient was discharged in satisfactory condition on July 4 after a course further complicated by pneumonia of the left lung base. In our opinion, the small doses of penicillin and streptomycin received by this patient and the short duration of this treatment eliminate these antibiotics as a cause of the diarrhea.

Comment.—That staphylococcic superinfection of the gastrointestinal tract after treatment with N-(pyrrolidinomethyl) tetracycline may not merely assume the relatively mild shape so far described but can also be overwhelming and rapidly fatal is shown by the last two cases which came under our observation.

CASE 5.—A 35-year-old man was admitted on July 31, 1959, with progressive arterial hypocirculation of the left leg, with intermittent claudication. Aortography revealed occlusion of both common iliac arteries, with filling of the femoral artery via the collateral vessels. Blood pressure was 135/95 mm. Hg, total serum cholesterol level was 394 mg.%, and left ventricular hypertrophia and myocardial damage was evidenced in the ECG. At operation on Aug. 1, the abdomen was entered through a lower midline incision and an endarterectomy of both common iliac arteries, supplemented by a left lumbar sympathectomy from the second lumbar to the first sacral vertebra, was performed. In addition, a fresh thrombus was removed from the left external iliac artery. The course of the four-and-one-half-hour operative procedure was normal, as was the circulation of the lower extremities after the operation. From Aug. 1 to 4, inclusive, a daily dose of 250 mg. of N-(pyrrolidinomethyl) tetracycline was administered intravenously. On Aug. 5, complications were ushered in by a rise in body temperature and pulse rate, a fall in systolic blood pressure, and vomiting. Diarrhea supervened on the next day. The clinical course,



Day		1	2	3	4	5	6	7	8	9	10
Urine	cc	600	600	500	350	?	3000	1300	1500	550	
specif. grav.		1034	1034	1030	1030		1012	1017	1018	1017	
Hemoglobin	g%	16				18,6				24,8	20,6
Leucocytes	mm³	8.800				4.400				6.700	14.400
Bilirubin	mg%	0.9				2.8				5.8	
Urea	mg%	27				20.	33				86
Protein	%	7.9					5.15				4.84
Sodium	meq	148				136			133		86
Potassium	meq	3.8				3.6			3.1		1.4
Alkaline reserve	meq	22.7				27.2			26.3		21.8
Reverin	mg	250	250	250	250	1000	1000	1000	1000	2000	1000
Erythromycin (i.v.)	mg								500	500	250
Chloramphenicol (i.v.)	mg					800	1200	400	800	1200	400
Whole blood	cc	1200						250	250	750	
Plasma	cc					5000	6000	4000	3000	3000	3000
Saline 0,9%	cc	2000	2000	2000	2000	2000	2000		1000	2000	1500
Glucose 5%	cc	1000	1000	1000	1000		2	4	4	3	1
KCl	gr					100	50	50	100	300	100
Hydrocortisone	mg									18	94
l-Nor-Adrenaline	mg										

Fig. 1 (case 5).—Clinical course, laboratory findings, and treatment of patient with subacute gastroenterocolitis due to Staph. aureus resistant to penicillin, streptomycin, tetracyclines, and the erythromycin group, and staphylococcic sepsis with irreversible shock.

treatment, and laboratory findings until the patient's death in irreversible shock on Aug. 10 have been graphically summarized in figure 1. Tracheotomy and artificial respiration were necessitated by progressive respiratory insufficiency, thought at first to be due to aspiration. Gram-positive cocci were demonstrated in stool smears on Aug. 6, the bacteriological diagnosis of Aug. 8 being Staph. aureus, which on Aug. 10, was shown to be resistant to not only penicillin, streptomycin, and the tetracyclines but to the erythromycin group of antibiotics as well. The clinical diagnosis was staphylococcic enterocolitis, the real magnitude of the complication not being recognized until autopsy.

Autopsy Findings.—The autopsy findings of the gastrointestinal tract and other organs in case 5 were as follows. Gastrointestinal tract: marked edema and hyperemia of the gastric mucosa, with numerous hemorrhages; intensive mucosal hyperemia of small intestine, with swelling of Peyer's patches (fig. 2). The colonic mucosa was intensely hyperemic, with numerous, partly confluent hemorrhages. Microscopically, the gastric mucosa was largely preserved, with some postmortem degeneration of surface epithelium. Mucosa and submucosa were edematous, showing compact, diffuse cellular infiltration with lymphocytes, some neutrophils, and numerous plasma cells. The reticulum cells of the lymph follicles were swollen. The serosa was thickened, with diffuse and circumscribed infiltrations of predominantly neutrophils. In places, the serosa was covered by exudate containing fibrin and leukocytes.

Other organs: there was staphylococcic sepsis, with multiple abscesses containing Staph. aureus in the myocardium, kidneys, and brain; bronchopneumonia, with abscess formation and septic thrombi in small pulmonary arteries and veins; fibrinopurulent tracheitis and acute hemorrhagic meningitis; acute swelling of the spleen; and diffuse fibrinous peritonitis. Other findings included generalized arteriosclerosis; hypertrophy and fatty degeneration of the myocardium; healed endocarditis of the aortic valve; pulmonary congestion; and cloudy swelling of the renal and hepatic parenchyma. Status: postendarterectomy of both iliac arteries, with no other abnormal local findings.

Clinicopathological Diagnosis.—The clinicopathological diagnosis in case 5 was subacute gastroenterocolitis due to Staph. aureus resistant to penicillin, streptomycin, tetracyclines, and the erythromycin group, and staphylococcic sepsis with irreversible shock.

Case 6.—A 56-year-old woman had a nephrectomy on the right for purulent pyelonephritis with hydronephrosis performed at another hospital in January, 1959. In the first week of August acute cholecystitis set in, with body temperatures up to 38.5 C (101.3 F), and the presence of gallstones was disclosed by cholecystography. Still in hospital, in another community, the patient was prepared for operation with up to four doses of 250 mg. of N-(pyrrolidinomethyl) tetracycline daily (a dose safe in the experience of other authors [10]), beginning Aug. 12. On Aug. 14, cholecystectomy was performed without difficulty, the gallbladder containing stones and empyema. No change in blood pressure occurred before, during, or immediately after operation, after which treatment with N-(pyrrolidinomethyl) tetracycline (exact dose unknown) was continued. On Aug. 15, the patient vomited two or three times, her course being otherwise apparently normal. On Aug. 16, however, she was found at 7 a. m. in profound shock with semicoma. Administration of transfusions and levarterenol bitartrate having failed to improve her condition, the patient was transferred for further treatment to the University Policlinic of Internal Medicine in Berne on Aug. 16 at 5 p. m. On arrival she was still in profound shock, in semicoma, distinctly exsiccated, and slightly icteric. Peripheral pulses and blood pressure were not recordable. The heart rate was 160 per minute, and the ECG evidenced sinus tachycardia and myocardial ischemia. Laboratory findings were as follows: hematocrit reading 59%, serum sodium level 140 mEq. per liter, serum potassium level 4.7 mEq. per liter, alkaline reserve 14 mEq. per liter, and nonprotein nitrogen level 100 mg.%. Treatment aimed at combating the shock and exsiccosis was instituted: a total of 250 ml. of whole blood, 250 ml. of human plasma, 75 ml. of a 15% human albumin solution, 3,500 ml. of 0.9% sodium chloride solution, 250 ml. of sodium lactate (1/6 M.), and 500 ml. of a 5% glucose solution together with 250 mg. of hydrocortisone and 150 mg. of levarterenol bitartrate was administered, until the patient's death on the next day at 5 p. m., Aug. 17.

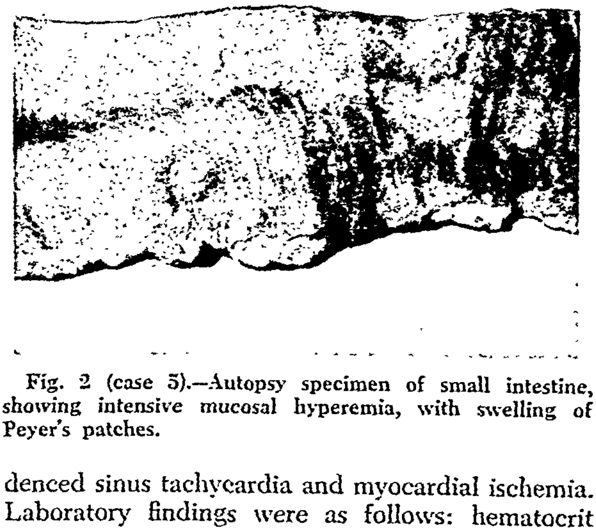


Fig. 2 (case 5).—Autopsy specimen of small intestine, showing intensive mucosal hyperemia, with swelling of Peyer's patches.

At first it had been possible to maintain the peripheral blood pressure at about 100 mm. Hg systolic, but on the last day of life the patient's course ran rapidly downhill. Shortly before death, the hematocrit reading was 61%, the nonprotein nitrogen level 135.6 mg.%, serum protein level

5.2% Gm.%, serum sodium level 144 mEq. per liter, serum potassium level 4.8 mEq. per liter, and alkaline reserve 11 mEq. per liter. On the morning of Aug. 17, the patient was seen in consultation by one of us (A. S.). With the experience of case 5 fresh in our minds, the diagnosis of staphylococcic enterocolitis with sepsis or toxemia, or both, immediately suggested itself. A rectal swab therefore was examined by means of a gram stain but showed only mixed bacterial flora, without preponderance of gram-positive cocci. At the insistence of the patient's son (a doctor), a small abdominal incision was made under local anesthesia to rule out the possibility of biliary peritonitis, with negative findings. Shortly before the patient's death, 500 mg. of erythromycin and 40 cc. of gamma globulin were administered. The direct cause of death was respiratory arrest. Other etiological possibilities discussed were acute hepatic necrosis or acute adrenocortical insufficiency. The uremia was considered secondary to preexisting impairment of renal function.

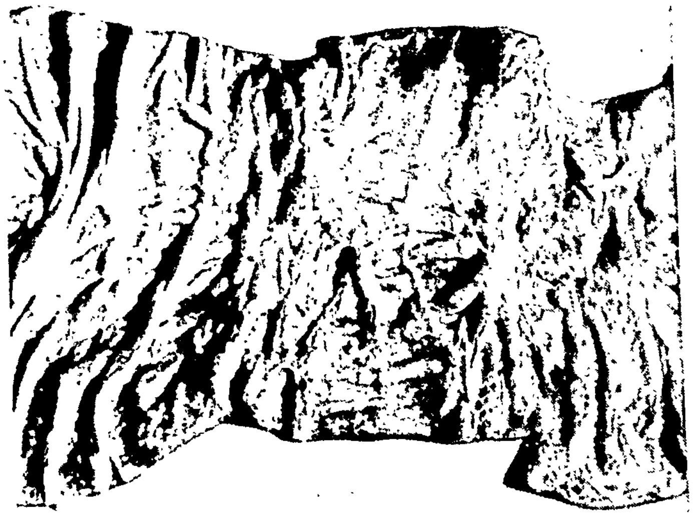


Fig. 3 (case 6).—Autopsy findings in small intestine, showing numerous mucosal ulcerations covered by yellowish, adherent membranes; mucosa between these membranes is intensely hyperemic.

Autopsy Findings.—Autopsy findings of the gastrointestinal tract and other organs in case 6 were as follows. Gastrointestinal tract: dilated stomach, with brownish, stool-like contents; mucosa with absence of normal relief, covered by extensive yellowish membranes, difficult to remove; and numerous petechial hemorrhages in the pyloric area. The duodenal mucosa was largely replaced by similar membranes, and numerous petechiae and ecchymoses were present. In the small intestine, numerous mucosal ulcerations covered by yellowish adherent membranes were found (fig. 3). The mucosa between these ulcers was intensely hyperemic. The lower ileum and the colon contained no membranes, and the mucosa was edematous and hyperemic. Microscopically, the gastric, duodenal, and jejunal mucosa were destroyed and replaced by thick fibrinous exudate containing a veritable blanket of staphylococci, besides nuclear débris and neutrophils. The jejunal submucosa showed extensive hemorrhages. All layers of the ileal and colonic walls showed extreme dilatation of blood vessels, which were filled with neutrophils.

Other organs: recent postcholecystectomy status and right nephrectomy seven months earlier; right-sided megaloureter, with abscess of the ureteral remnant; anemia and cloudy swelling of the left kidney; cloudy swelling and central fatty degeneration of the liver; congestion of internal organs; arteriosclerosis; and generalized icterus.

Bacteriological examination of intestinal contents, spleen, and ureteral abscess yielded Staph. aureus, resistant to penicillin, streptomycin, and the tetracyclines.

Clinicopathological Diagnosis.—The clinicopathological diagnosis in case 6 was acute necrotizing gastroenteritis, with overwhelming intoxication and irreversible shock, due to Staph. aureus resistant to penicillin, streptomycin, and the tetracyclines.

Comment

The clinical course of the patient in the last case merits special attention. Without diarrhea ever appearing and without significant findings in the rectal swab, the patient developed shock and paralytic ileus and died in irreversible shock due to overwhelming intoxication. Although this clinical picture has been observed in cases of staphylococcic enteritis due to other antibiotics as well, and is thus not specific for N-(pyrrolidinomethyl) tetracycline, the route of administration of the latter drug might well further deflect attention from the possibility of gastrointestinal superinfection, with loss of invaluable time. In the case presented, probably no clinical suspicion would have arisen but for the occurrence of the death of another patient (case 5) a few days earlier. Without an autopsy, the etiology would in any case have remained a mere hypothesis. The therapeutic difficulties and the grave prognosis of the patient in septic shock[11] are amply illustrated by the fate of these two patients.

The incidents just described will, we hope, make it clear that staphylococcic enterocolitis after treatment of surgical patients with N-(pyrrolidinomethyl) tetracycline is a risk not to be neglected, nor do we think that the explanation of this fact need be sought far. The stool concentrations of tetracycline of from 5 to 10 mcg. per gram found after administration of N-(pyrrolidinomethyl) tetracycline,[3] even if 10 times lower than those resulting from oral intake of the equivalent tetracycline dose, are capable of suppressing sensitive intestinal bacteria since the tetracyclines show an in vitro bacteriostatic effect against gram-negative organisms in concentrations ranging from 1.5 to 3.5 mcg. per gram.[12] From a bacteriological viewpoint, intravenous treatment with N-(pyrrolidinomethyl) tetracycline, too, may thus create favorable conditions for superinfection of the gastrointestinal tract with tetracycline-resistant staphylococci, which by now amount to about 80% of all hospital strains.[13]

Beyond doubt, however, the antibiotic cannot be incriminated as the sole causative factor in the etiology of these complications. The various stresses and strains put on the surgical patient, and more specifically on his gastrointestinal tract—purgation, anesthesia, operation, and postoperative fasting—conceivably amount to another predisposing factor of no small importance. Experimental work[14] has shown that in staphylococcic infection defense mechanisms of the host may be altered at will within a few hours, disturbances of nutrition and metabolism, endotoxins produced by other microorganisms, acute fasting, and subclinical allergic reactions being among the factors hampering the defense. Moreover, any surgeon knows that patients who have been subjected to intra-abdominal operations or procedures involving the retroperitoneum, including lumbar sympathectomy, as was the case in five of our six patients, are especially prone to suffer from sluggish postoperative peristalsis with consequent intestinal dilatation, which has recently been shown[15] to be of considerable importance for the development of experimental pseudomembranous enteritis. These general considerations and experimental findings are in agreement with recent clinical experience, according to which staphylococcic enterocolitis is, above all, a menace to the surgical patient. To our knowledge, no such complication of treatment with N-(pyrrolidinomethyl) tetracycline has so far been encountered in patients suffering from purely medical ailments. As to patients not hospitalized, the relatively low rate—still in the vicinity of 5%[16]—of tetracycline-resistant staphylococci in the population at large might be expected to reduce the risk of such incidents to low proportions. By contrast, anaphylactic shock[4] may occur in the patient's home as well, and it would seem prudent to take the necessary precautions for dealing with this complication anywhere.

Summary and Conclusions

We want to emphasize that the publication of this report of light as well as fatal cases of staphylococcic enterocolitis in surgical patients after intravenous treatment with N-(pyrrolidinomethyl) tetracycline (Reverin [Germany], Syntetrin [U. S. A.]) is not intended to discourage the use of this remarkable drug, which undoubtedly possesses many advantages and which has proved these to the satisfaction of other authors and ourselves. We are obliged to make it clear, however, that—at least as far as patients recently operated on are concerned—the assumption that N-(pyrrolidinomethyl) tetracycline does not derange the intestinal flora and carries no appreciable risk of the occurrence of staphylococcic enterocolitis cannot be considered valid and that, therefore, patients thus treated must be watched just as closely for this complication as those receiving any other tetracycline derivative. Finally, the threat of lethal superinfection defying every form of therapy once again proves that no antibiotic should ever be administered in the absence of sufficient indications for its use.

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The staff of the University Policlinic of Internal Medicine placed the history of case 6 at the author's disposal.

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CLINICAL NOTES

HYPOPROTHROMBINEMIA DUE TO PROPYLTHIOURACIL THERAPY

REPORT OF A CASE

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Thiouracil therapy of thyrotoxicosis has been well established for a number of years. Tapazole (Methimazole) and propylthiouracil are the two drugs in this group that have been extensively used. A number of toxicity reactions to these drugs are well known to the medical profession. However, purpura caused by severe hypoprothrombinemia due to propylthiouracil therapy in a rare complication and is not well known to physicians. There are apparently only two previous cases of this form of toxicity reported in the literature in the United States. Craddock and others[1] reported in 1951 a case of a 16-year-old girl who developed a severe bleeding diathesis while being treated with propylthiouracil. A low prothrombin time was the only abnormality noted. Mirrer[2] in 1955 reported a second case in a 43-year-old woman who had been on propylthiouracil therapy for about six months.

A 33-year-old woman had been under continuous medical observation since 1952. At her first visit she stated she had been treated for "nerves" for many years. Her symptoms included restlessness and insomnia. She had been married for four years and had had several miscarriages. The gynecologist could find no obvious cause for her frequent miscarriages. Physical examination showed a possibly slightly elevated blood pressure, 140/90 mm. Hg, some tachycardia, xanthomatous deposits around both eyelids, and some exophthalmus. The exophthalmus had been present for a number of years. Blood sugar levels were noted to be top normal. Evaluation of thyroid function had been made by her gynecologist, and it was reported as normal. These tests were repeated and indicated normal basal metabolic readings and normal protein bound iodine values. Her history indicated that she was a member of a family whose members all suffered from severe anxiety. Her mother had died of multiple myeloma, and her father suffered from hypertensive vascular disease.

The patient was treated symptomatically for several years. In 1952 and 1953 she had two more miscarriages, and finally in 1953 she adopted a child and gave up further attempts at conception. She was examined at regular intervals from 1952 to 1957. It was presumed that her symptoms, viz., anxiety, palpitation, and dizziness, were part of a pattern of chronic anxiety. The only abnormalities noted were a slightly elevated white blood cell count and top normal blood sugar level. An endocrine disturbance of pituitary origin was considered but not proved. In September, 1957, her ophthalmologist reported some concern about her exophthalmus, and her physical condition was again checked. The findings were identical to those previously found. Measurement of basal metabolic rate was —1 and —3%, respectively, and her protein-bound iodine value was 4.7 mg.%. Roentgenogram of the skull revealed a normal pituitary fossa. There was some evidence of a thickening of the inner table of the frontal bone.

Although a diagnosis of hyperthyroidism had not been proved by laboratory tests, the patient was placed tentatively on antithyroid therapy on Dec. 30, 1957. Therapy consisted of propylthiouracil and of a small dose of thyroid to suppress the activity of the pituitary gland and to possibly affect her exophthalmus. Response to therapy was dramatic. One month later the patient reported that she felt much better; she was sleeping better and was not as nervous. The affect on her exophthalmus was uncertain, but the general impression was that it was somewhat improved. In May, 1958, after five months of therapy, an attempt was made to reduce the dosage of propylthiouracil. In July the patient felt her nervousness had increased, and the dosage of the drug was slightly increased.

On Feb. 5, 1959, she returned complaining that for several days she had noted an aching in her back and that her menstrual period had been unusually heavy and prolonged. A few purpuric spots were also noted. A blood cell count and platelet count gave normal findings. Two days later she was admitted to the hospital because she had begun to bleed from her gums; she had backache and fever, and the purpuric spots increased in number. On her admission to the hospital it was noted that her blood cell count had dropped somewhat, but the striking abnormality was a prothrombin time of 2% of normal. She was given vitamin K parenterally; several hours later her protrombin time had increased to 28% of normal, and she began to improve rapidly. Her temperature and sweating gradually subsided over a period of about a week, and she was discharged with a normal prothrombin time.

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Aside from the propylthiouracil, the only drugs that she had taken were acetylsalicylic acid and meprobamate. The acetylsalicylic acid was taken after her purpura had been noted and was, therefore, probably not the cause of her hypoprothrombinemia. In order to prove the causative relationship of propylthiouracil to her hypoprothrombinemia, it seemed advisable to readminister the drug, but the severity of her reaction made such treatment inexpedient. However, acetylsalicylic acid and meprobamate were both administered over a period of several weeks without producing hypoprothrombinemia.

Comment

It seems likely that bleeding in this patient was caused by hypoprothrombinemia and that the propylthiouracil was responsible for this condition. Vitamin K therapy resulted in dramatic improvement. In both of the other reported cases [3] vitamin K did not seem to be as effective. In Craddock's case the patient was given fresh thrombin-free serum, and immediate improvement was noted. They believed the defect was caused by a deficiency of accelerator globulin. It may be of significance that our patient's total globulin level was somewhat low.

Summary

A patient had a bleeding diathesis caused by a severe hypoprothrombinemia. Propylthiouracil was the apparent cause of the depressed prothrombin time. This toxic effect of propylthiouracil is not well known. Only two other cases have apparently been reported. Vitamin K therapy was effective in relieving the hypoprothrombinemia in this patient.

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AINHUM—OCCURRENCE OF A CASE IN NORTHERN OHIO

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Since the first description of ainhum (dactylolysis spontanea) by Clarke [1] in 1860, many case reports have appeared, primarily from the tropical areas and the southern part of the United States. Until 1945, only about 50 cases had been reported from the United States; at the time of writing somewhat more than 100 have been reported.[2]

Whether the condition is actually rare in the United States or simply not well recognized by the medical profession is not known. Most authors believe the latter to be true. The first case seen at the Cleveland Veterans Administration Hospital in the 13 years of its existence is reported herein. One case was previously diagnosed at the University Hospitals of Cleveland (1944), while no cases have been seen at the Metropolitan General Hospital (Cleveland City Hospital) in the past 35 years.

The term "ainhum" is derived from an African word meaning "to saw." Ainhum is literally that: a progressive autoamputation of a toe, usually the fifth. The condition occurs principally in male Negroes in warm climates but has been reported in male and female Puerto Ricans, South Americans, and Caucasoid Americans. It has been reported as far north as New York and Pennsylvania and recently was reported for the second time in England.[3] In 1953, a report of "pseudoainhum" was recorded as a congenital defect of the fingers and wrist in a Caucasoid female infant.[4]

The clinical picture is unmistakable unless seen for the first time. The fifth toe invariably is involved first; occasionally the fourth toe may become involved later. A small, painless crease develops in the digital fold at the base of the fifth toe. This slowly deepens and widens, with formation of a linear fibrous constricting band encircling the entire digit. As this fibrous band further tightens and constricts, the toe progressively amputates itself.

Report of a Case

A forty-five-year old Negro man was admitted to the Cleveland Veterans Administration Hospital on Aug. 26, 1959, with the complaint of pain in his right fifth toe. He had been in good general health until about three years prior to this admission, when he noted the insidious onset of pain in his right fifth toe. The pain progressed in intensity and was followed one year prior to admission by a constriction of the toe, together with a break in the skin. This constriction progressed in spite of the local application of hot soaks, various ointments and lotions, as well as antibiotics. He was then referred to this hospital for further therapy.

From the departments of surgery, Cleveland Veterans Administration Hospital, University Hospitals of Cleveland, and Western Reserve University School of Medicine.

The patient was born in southern United States but had spent most of his adult life in Ohio. While in the military service from 1942 to 1945, he had been stationed in Hawaii and on the island of Tinian in the South Pacific for three months. During this period he had fungous infections of the feet ("jungle rot"), more severe on the left foot, and he was transferred back to the United States for therapy. The condition promptly subsided and he has had no recurrence. There was no family history of foot disorders.

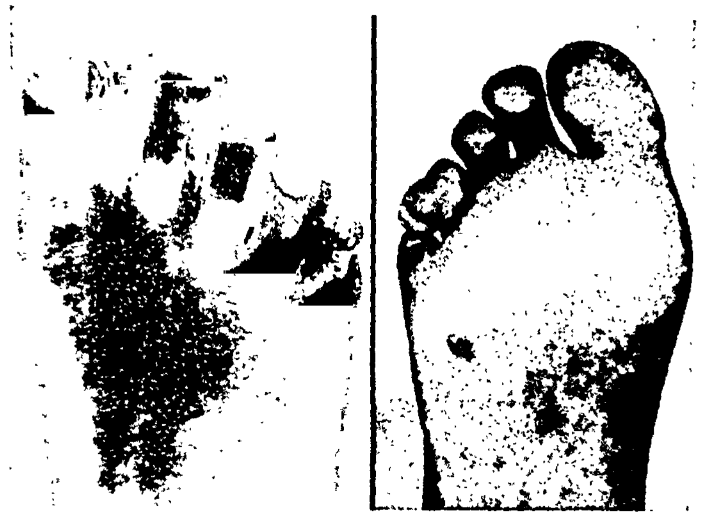

Fig. 1.—Ainhum: photographs of right foot: *left,* dorsal view; *right,* plantar view.

Physical examination revealed a well-developed, well-nourished, middle-aged man in no apparent distress. His right fifth toe had a bulbous appearance in the distal portion, and there was a linear constricting band in the digitoplantar fold (fig. 1). There was no evidence of gangrene. The toe was extremely tender to palpation. All peripheral pulses were palpable, and the rest of the physical examination was unrevealing. Results of a complete blood count and urinalysis were within normal limits and that of a serum test for syphilis was negative. Roentgenograms of the right foot revealed bone atrophy and incomplete destruction of the distal portion of the proximal phalanx of the right fifth toe (fig. 2).

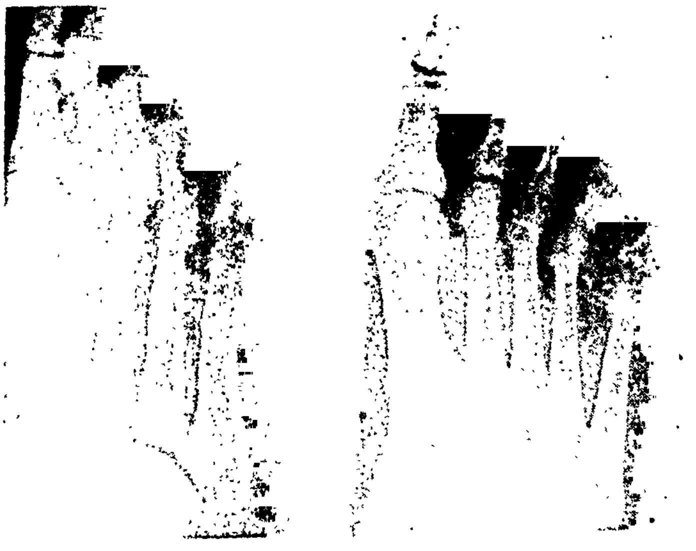

Fig. 2.—Roentgenogram of right foot showing bony destruction of phalanges of fifth toe.

On Aug. 31, 1959, an amputation of the right fifth toe was performed under spinal anesthesia (fig. 3). The patient's postoperative course was uneventful, the wound healed by first intention, and he was discharged from the hospital on his 10th postoperative day.

Etiology, Symptoms, Pathology, and Treatment

Etiology.—The cause of ainhum is unknown. Racial and hereditary factors seem to be most important. Norton[2] mentioned some of the etiological factors which have been considered. Among these, epidermophytosis, leprosy, localized scleroderma, localized endarteritis, spirochetal infections such as yaws and syphilis, chronic osteomyelitis, endocrine dysfunction, and the wearing of constrictive bands about the digits have all been incriminated. Recently Auckland, Ball, and Griffiths[3] stressed the importance of chronic nonspecific inflammation of the deep fascial layers, with erosive arthropathy and periostitis. There are no theories to explain why the disease is confined predominantly to the male Negro and to the fifth toe.

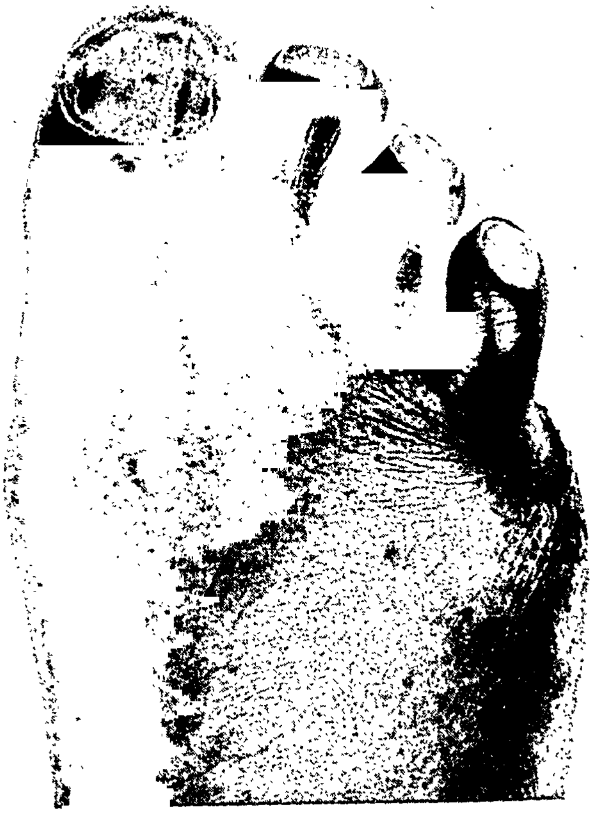

Fig. 3.—Photograph of right foot, taken one week after amputation of fifth toe.

The first sign of the condition is usually the development of a small, painless crease at the base of the fifth toe. There may or may not be a history of infection or trauma to the affected digit. Burch and Hale[5] reported that patients may note an itching of the toe early in the disease. A small papule, with or without vesicular formation and ulceration, may form in the region of the initial trauma. Secondary infection, which is usually chronic, then supervenes, and at this point the patient begins to note varying degrees of pain. A linear, fibrous, constricting band gradually develops to encircle the entire digit. As the disease progresses, the bone is gradually absorbed and a loosely attached bulbous appendage, distal to the sulcus, remains. During this stage of the disease, pain usually becomes severe and is aggravated by walking or by movement of the digit. If untreated, the bulbous distal portion of the digit will progressively amputate itself.

Pathology.—Grossly, the distal portion of the toe is bulbous and firm. The top of the toe may be edematous, scaly, and pale tan in color. A fibrous band constricts the proximal phalanx. Histologically, there is hyperkeratosis of the epidermis. The dermis is fibrotic and chronically inflamed. There are fibrosis of the corium and bone atrophy. The walls of the blood vessels are thickened and the lumens narrowed, but there is no evidence of obliteration. The nerves are not involved (fig. 4).

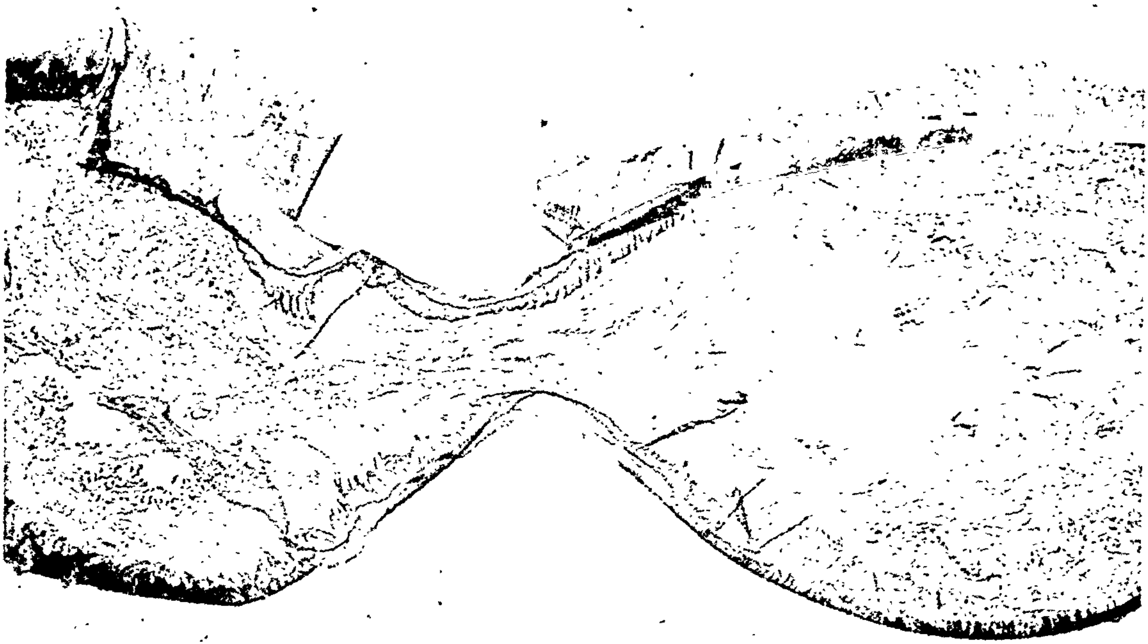

Fig. 4.—Photomicrograph of longitudinal section through right fifth toe, low-power view. Note fibrous constricting band in center of field.

Treatment.—No effective therapy for ainhum has yet been devised which saves the toe. Excision of the constricting band has been frequently performed but, in general, without success. Recently Brown [6] reported the successful use of multiple Z-plasties on the constricting band with preservation of the toes. Occasionally, when pain is not severe, some digits have been allowed to progress to autoamputation.

We believe that the treatment of choice is amputation of the affected digit at its base. This has proved successful over a number of years, with good healing of the wound and a short period of hospitalization. Loss of this digit is not disabling to the patient.

Summary

A case of ainhum was reported from northern Ohio, an area in which the condition is rare. The patient, a Negro man, had spent three months on the island of Tinian in the South Pacific during World War II. Amputation of the affected toe resulted in prompt healing. A review of the various measures advocated for treatment of this condition leads us to recommend amputation as the most effective form of therapy at present.

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SIMPLE DEVICE FOR PRACTICING VASCULAR ANASTOMOSIS

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Every surgeon should be able to anastomose or repair blood vessels. This knowledge is essential, since he may be called on at any time to perform such a procedure. Restoration of continuity of a blood vessel may enable him to save a limb or avert some other catastrophe. The techniques should be within the capability of any surgeon.

The methods, though not difficult, require a knowledge of the use of the instruments used in vascular surgery and actual practice in doing anastomoses or repairs. In the event that specialized instruments are not available when needed, the surgeon who has learned and practiced the techniques with the instruments ordinarily used in vascular surgery should be able to substitute other instruments or materials. It is essential to have proper suture material, preferably 00000 or 000000, nonabsorbable suture, with a swedged-on curved needle. An arterial silk which meets these requirements is available.

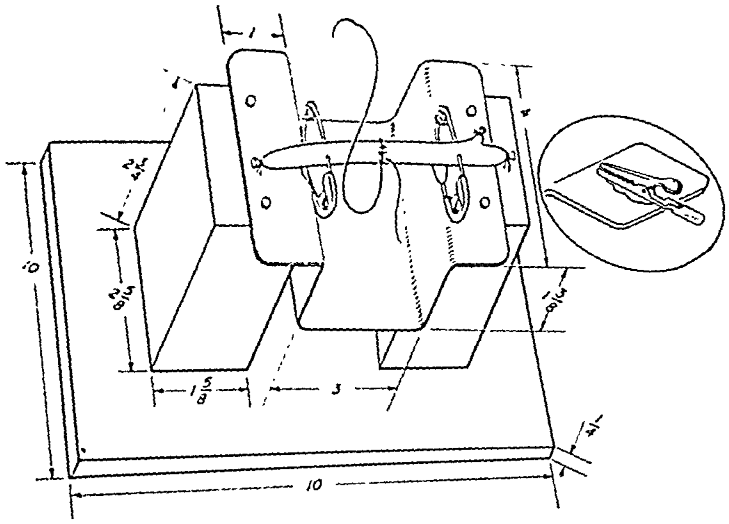

Fig. 1.—Simple device for practicing anastomoses.

Physicians who wish to perfect their skill in these procedures do not always have access to experimental animals in which conditions are similar to those in human beings. It is, however, ordinarily possible to obtain stripped-out blood vessels from animal or autopsy sources. These sections of vessel may be held in a simple jig in such a way as to simulate the situation which may present at surgery (fig. 1). The surgeon can then leisurely practice any number of techniques and gradually improve his ability and speed.

The device, which the surgeon can easily construct himself, is mounted on a piece of ¼ in. plywood 10 in. square. Two wood blocks, 2¾ in. high by 2⅝ in. wide by 1⅝ in. thick, can be cut from standard 2-by-4-in. stock and are mounted on the plywood base 1⅞ in. from two opposite edges with four 1-in. no. 6 flat-head wood screws, which are screwed into the underside of the base. A strip of light-gauge galvanized sheet metal is cut 7¾ in. long and 4 in. wide, with rounded corners. It is bent into a trough shape so that it fits between the wood blocks. It is then depressed between the blocks 1⅜ in., the protruding edges are bent over the blocks, and it is held in place with four ½-in. round-head screws. The metal work surface will not corrode and cleaning of the device is easy. Two 2-in. safety pins are then soldered to the upper opposing edges of the metal trough in such a way that the pointed ends of the pins freely open and close. Battery alligator clips may be substituted for the safety pins if desired (see fig. 1, *insert*). A more elaborate device which has one movable end and offers more flexibility for anastomosing larger and more complex specimens has been designed and is available (fig. 2).

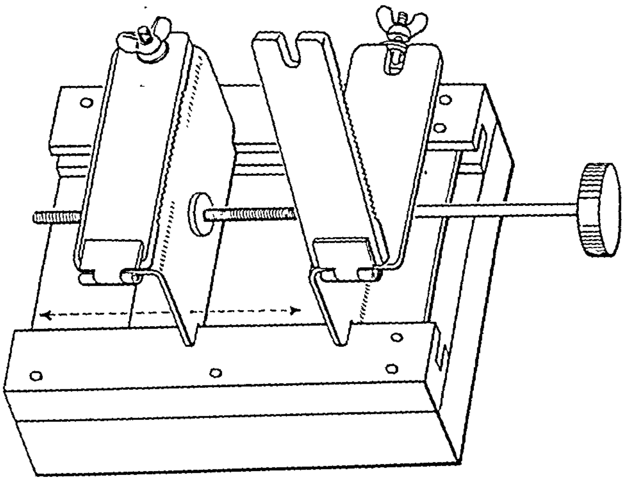

Fig. 2.—Jig for practicing anastomoses with one movable side.

The sections of blood vessel are attached by the safety pins or clamps so that their free ends just oppose each other. The anastomosis or repair is accomplished by any of the accepted techniques.[1] When the anastomosis or vessel repair is complete, hemostats may be applied on either side of the suture line and the integrity of the approximation tested for leakage. This is done by introducing a 26-gauge hypodermic needle attached to a syringe into the side of the vessel and forcing water from the syringe into the vessel lumen. Success or failure will be obvious, although in dead tissue there may be some leakage even with good technique. In living tissue clotting will usually occlude minute defects.

Summary

Two devices for practicing anastomosis or repair of blood vessels are illustrated. Techniques learned

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From St. Luke's Hospital.

in this simple way will greatly facilitate and aid the surgeon when he is called on to carry out this procedure in human beings. The device is useful for teaching technique to members of the staff. Both devices may also be used for practicing suturing of tendons or nerves or anastomosing artificial arterial graft materials.

504 Carnegie Medical Bldg. (6) (Dr. Brown).

Pemco, Inc., Brecksville, Ohio, supplied the device shown in figure 2.

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INJURY TO THE LIVER IN AUTOMOBILE ACCIDENTS

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On examination of any victim of an automobile accident, the possibility of injury to the liver and bile ducts should be considered, especially in the presence of a rib fracture on the right side of the thorax. Tenderness on compression of the lower portion of the rib cage on the right side plus pain referred to the right shoulder in the absence of rib fracture, in a patient after an automobile accident, are ample evidence for the diagnosis of rupture or laceration of the right lobe of the liver.[1]

Signs and Symptoms

In cases of ruptured liver, those victims who are not killed immediately show the signs and symptoms of intraperitoneal hemorrhage, including pain, weakness, pallor, restlessness, dyspnea, rapid pulse, fall in blood pressure, shifting dulness, subnormal temperature, anemia, leukocytosis, abdominal tenderness and rigidity, and absent or decreased bowel sounds. The escape of blood and bile into the peritoneal cavity can result in rapidly progressive shock, which, within a short time, is irreversible. Nausea and vomiting may be present. The vomitus may be bloody from hemorrhage throughout the biliary system passing through the common duct into the duodenum.

If the patient survives for a few days, mild jaundice usually becomes manifest. Radiation of pain to the right shoulder is almost the rule if the superior surface of either lobe has been ruptured. In patients with liver injury pain persists in the upper abdomen and increases with movement, often strikingly so on attempted deep inspiration. The appearance of a mass in the right upper quadrant, caused by either displacement of the liver downward from an expanding accumulation of clot between the diaphragm and the liver or hemorrhage in the subhepatic area, is commonly associated with shock. These are unmistakable signs of advanced and serious liver fracture. Several authors[2] advocate the use of abdominal tap with a spinal puncture needle in all four quadrants of the abdomen as a diagnostic aid in suspected cases of ruptured viscus. Negative findings of such a tap, however, are not conclusive evidence of lack of injury. Since liver trauma may vary from mild to very severe, it is imperative that the surgeon make repeated, careful examinations to detect variable significant clinical signs.

Most surgeons agree that a patient with a ruptured liver should have drainage for a few days to avoid intraperitoneal leakage of bile and bile peritonitis. Intrahepatic drains are advocated in patients with deep laceration of the liver to prevent hemobilia.[3] At operation, if hemorrhage from the liver is still active, control can be obtained by pressure of the thumb and finger over the portal vein and hepatic artery at the foramen of Winslow, in the free edge of the hepatoduodenal ligament. Repair of the liver is accomplished with deep wide mattress sutures, use of hemostatic agents such as Gelfoam in combination with sutures, use of omentum, and, occasionally, resection of the injured part. While adequate replacement of blood by transfusion is frequently required, the use of intra-abdominal blood for retransfusion is contraindicated, since such blood contains bile and causes serious reactions.

In the differential diagnosis of nonpenetrating abdominal injury, hemorrhage into the rectus muscle or tearing of the epigastric blood vessels can mimic injury to a viscus in the right upper quadrant. Attempts at flexion from the supine position will cause pain, but tenderness on palpation will be

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less in the flexed position. A history of trauma will exclude possibilities of nontraumatic intra-abdominal disease, although such conditions may arise concomitantly and may or may not be due to trauma, e. g., acute cholecystitis or pancreatitis. Pancreatic trauma, duodenal rupture, retroperitoneal hematoma, kidney trauma, and ruptured spleen may all contribute to difficulty in diagnosis.

Patients involved in automobile accidents may be unaware of the degree of abdominal injury incurred, and there may or may not be evidence of visible abdominal trauma. At the beginning, pain may be absent or minimal but symptoms may develop later. The patient must be carefully observed and the possibility of liver injury must be kept in mind.

Report of a Case

A 39-year-old man was admitted to the hospital at 8 p. m. on May 17, 1959. He stated that he had been in an accident at 9 p. m. on May 16, when his automobile hit the rear of a car ahead. He sustained abrasions but otherwise did not seem injured. At 1 a. m. on the day of admission he was awakened by generalized abdominal pain which persisted and became more severe. On physical examination his color was good. There were abrasions of the lower lip, right wrist, and right knee. Rigidity and tenderness were present over the entire abdomen. His pulse was regular at 88 beats per minute. Roentgenograms of the abdomen did not show free air. Serum amylase level was 26 Somogyi units. His leukocyte count was 14,200 per cubic millimeter and his hemoglobin level was 14 Gm.%. Twelve hours later, the hemoglobin level was 12.1 Gm.% and the leukocyte count 12,650 per cubic millimeter. Abdominal findings were unchanged, except for less tenderness. The next morning abdominal rigidity and tenderness were still present and the hemoglobin level was unchanged. At operation a 2.5-cm. laceration of the liver at its junction with the falciform ligament was found, and there was fresh bleeding from the torn surface, with about 500 cc. of dark blood in the peritoneal cavity. The liver laceration was repaired with chromic sutures and absorbable gelatin sponge (Gelfoam). Drains were placed in the peritoneal cavity. The patient made an uneventful recovery.

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SULFADIMETHOXINE IN UPPER RESPIRATORY INFECTIONS

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In this day of broad-spectrum antibiotics and their mass use against all forms of infectious processes, it is refreshing to refocus attention on the oldest and best class of antibacterial drugs, the sulfonamides, whose clinical effectiveness is well known. Recent advanced pharmaceutical research in this field has yielded products of greater safety, which has led to renewed awareness of the true value of these agents in the armamentarium of the practicing physician.

Toward this end, I have recently undertaken the evaluation of a new long-acting sulfonamide, sulfadimethoxine (Madribon), in the routine therapy of common respiratory infections in patients seen in daily practice. Previous reports on the use of this drug for respiratory illnesses have indicated it to be safe and efficacious.[1] For reliable evaluation of a drug, it is necessary to compare the results of many studies conducted by independent investigators from different localities. Only in this way can a true picture be obtained of the therapeutic agent in relation to resistance patterns of the infectious organisms. Leming and others[2] conducted such a survey of organism-resistance patterns according to geographical areas. They found that where a particular antibiotic had been extensively used, the organisms commonly encountered developed a resistance to the antibiotic. To my knowledge, the following study on sulfadimethoxine is the only one from the area of Cape Girardeau, in southeastern Missouri.

This work was done on a random sample of patients suffering from respiratory illnesses during the winter and spring months. In this area, acute respiratory illness has proved to be most prevalent during these seasons. Adult and pediatric groups were studied with no attempt whatever at selection of cases.

Materials and Methods

Data were obtained on 106 patients treated with sulfadimethoxine for a variety of respiratory and associated conditions–including pharyngitis, tonsillitis, otitis media, rhinitis, and sinusitis. After an initial careful examination and establishment of a preliminary diagnosis, cultures of the causative organism were grown; standard sensitivity studies were carried out with use of disks for tetracycline (Achromycin, Panmycin, Polycycline, Tetracyn, Tetracyn V), erythromycin (Erythromycin, Ilotycin), penicillin, streptomycin, triple sulfonamides, and sulfadimethoxine.

The patients' ages ranged between 3 months and 73 years. There was a slightly greater number of males (57 males and 49 females). All adult patients received a priming dose of 2 Gm. of sulfadimethoxine, given orally in tablet form, followed by administration of 1 Gm. daily. Children over four years of age received an initial dose of 1 Gm. of the drug in a suspension, with subsequent dosage of 0.5 Gm. given every 24 hours; those under four years of age received 0.25 Gm. of sulfadimethoxine daily. No patients were treated for less than one week; some received sulfadimethoxine therapy for as long as one month.

Results were considered excellent or good depending on the length of treatment time required for the patients to become asymptomatic. If it was necessary to administer an antibiotic before improvement was shown, results were considered poor.

Results

Streptococcus pyogenes was the most frequently isolated organism, followed in order of frequency by Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, and nonhemolytic Staphylococcus epidermidis. In vitro tests showed that 75.4% of the organisms isolated were sensitive to sulfadimethoxine, the remaining 24.6% showed resistance (table 1).

Table 1.—*Response of Cultured Organisms to Sulfadimethoxine*

Organism*	Response Sensitive, No	 Resistant, No.
Streptococcus pyogenes	23	3
Klebsiella pneumoniae	20	6
Pseudomonas aeruginosa	17	5
Escherichia coli	7	3
Staphylococcus aureus	7	2
Staphylococcus epidermidis	6	7
Total	80	26
% of total	75.4	24.6

* Listed in order of frequency.

Ninety-four patients (88.7%) had a good or excellent response to sulfadimethoxine treatment, and 12 (11.3%) required additional medication. Forty of 44 patients with pharyngitis had good or excellent results. Similarly, 33 of the 36 patients with tonsillitis, 10 of 14 with otitis media, 7 of 8 with rhinitis, and all of those with sinusitis had good or excellent results; in these, a definite clinical improvement was noted within 24 hours after administration of this drug. The remaining patients responded poorly to sulfadimethoxine medication.

There was no evidence of nausea, vomiting, skin rash, urticaria, crystalluria, or hematuria and no change in the hemogram in any of the patients. Considering these results, I felt justified in trying the drug for prophylaxis in nephritis. Thus, I administered 0.5 Gm. of sulfadimethoxine daily to a 13-year-old nephritic boy who was unable to take penicillin orally because of a demonstrated sensitivity to it. After two days of sulfadimethoxine therapy, the patient suddenly developed a gastrointestinal disturbance characterized by nausea, vomiting, and diarrhea. The medication was discontinued, and he had no further difficulty.

Report of Cases

Three typical case histories taken from this study are presented. They are the histories of (1) a patient refractory to other antimicrobial therapy, but who responded to sulfadimethoxine; (2) a patient with acute purulent otitis media treated with sulfadimethoxine; and (3) a patient with parotitis complicated by acute pharyngotracheitis.

Case 1.—A 24-year-old college student was first seen with complaints of chills and fever, a productive cough, and rhinorrhea of six days' duration. He had previously been treated elsewhere with 250 mg. of erythromycin given four times a day for five days, with no apparent improvement. Examination revealed boggy nasal mucous membranes, typical of secondary rhinitis, and heavily infected, swollen, granular appearing posterior pharynx. The ears were normal, and the chest was clear; urinalysis was negative. Blood studies indicated a left shift with a white blood cell count of 18,400 per cubic millimeter but no anemia. Cultures for organisms were obtained from the throat; Staphylococcus epidermidis, nonhemolytic, reported 48 hours later, was questionably sensitive to sulfadimethoxine and resistant to erythromycin. The patient was afebrile and, by this time, showed marked clinical improvement. Four days after the beginning of therapy, he was able to return to school and has progressed well since.

Case 2.—A 2½-year-old boy had a temperature of 103.6 F (39.7 C), taken rectally, and an earache of 12 hours' duration in the right ear. On exam there was marked erythema, bulging, and edema of the right tympanic membrane, with loss of the light reflex and usual landmarks. The left drum was normal. A thick, mucopurulent drainage was present in the posterior pharynx. The remainder of the examination was not remarkable, and the urine was negative on routine analysis. The diagnosis of acute purulent otitis media of the right ear was entertained; after the usual preparation, using local cocaine drops, the ear drum was incised and yielded considerable purulent material, which was cultured. The gram stain, after 48 hours growth, revealed a beta hemolytic streptococcus which was sensitive to sulfadimethoxine as well as the other antimicrobial agents, except penicillin and streptomycin. After myringotomy, the child was given sulfadimethoxine suspension, 1 Gm. initially and 0.5 Gm. per day for 10 days. Twice the dosage usually used in this age group was given because of the severity of infection. Within 24 hours, all fever had subsided, and, 48 hours after initiation of therapy, the child was again playful and seemingly well. When seen a month later, he had no recurrence or other difficulty.

Case 3.—A 5-year-old girl with symptoms of coryza of three days' duration began to develop enlargement and tenderness of the right parotid gland. The initial examination revealed a typical acute parotitis, and the history revealed a known contact about three weeks prior to the appearance of symptoms. Routine supportive therapy was recommended at the first visit, but no antimicrobial agents were administered. However, when she was seen three days later, there was a sudden increase of temperature to 102 F (38.8 C), taken orally, and complaint of sore throat. This examination revealed an acute bilateral follicular tonsillitis, secondary to parotitis, and cultures for organisms were taken from the tonsillar area. These cultures after incubation revealed a Staphylococcus aureus organism which was resistant to sulfadimethoxine. However, prior to the culture report, the child had been given sulfadimethoxine suspension, 1 Gm. initially and 0.5 Gm. daily thereafter. Since he was afebrile and clinically appeared better by the time the culture report was received, medication was continued for another week. At that time, the patient was well, and all traces of her acute illness had vanished.

Table 2.—*Response of Patients to Sulfadimethoxine Therapy by Diagnosis*

	Diagnosis, No.					Total	
Response	Pharyngitis	Tonsillitis	Otitis Media	Rhinitis	Sinusitis	No.	%
Good to excellent*	40	33	10	7	4	94	88.7
Poor†	4	3	4	1	0	12	11.3
Total	44	36	14	8	4	106	100.0

* Definite improvement shown in first 24 hours of therapy.

† Necessary to administer an antibiotic before improvement was shown.

Comment

From this study, several important conclusions can be drawn. There is a divergence of opinion on the reliability of in vitro studies as a guide to clinical response to sulfonamides or antibiotics. Some [3] find sensitivity tests a valuable basis for choosing the best drug in a given infection, whereas others [4] have found little correlation between in vitro tests and clinical response to sulfonamides. Since only 75% of the cultures were shown to be sensitive to sulfadimethoxine, a significant difference in clinical results was not to be expected. Yet, 88.7% showed a good response to treatment with sulfadimethoxine alone. Apparently, sensitivity studies in vitro are not a good index of clinical response.

Another important feature of this drug not pointed out previously is its rapid action. Within 24 hours, there was definite clinical improvement in those patients showing good or excellent response (table 2). The toxicity of sulfadimethoxine is almost nil. Only one of these patients manifested any side-reactions, and these were very mild. The hemograms failed to reveal toxic effects. Furthermore, the importance of the cost of medication should not be overlooked in evaluating its use in such widespread conditions as upper respiratory infection. While it is equally as effective as other antibacterials, sulfadimethoxine is much less expensive.

Summary

One hundred and six patients with upper respiratory or allied infections were treated with sulfadimethoxine for periods ranging from one week to one month. Adults received 2 Gm. of sulfadimethoxine initially followed by 1 Gm. daily. Children over 4 years of age received as the priming dose 1 Gm. of the drug in a suspension and 0.5 Gm. as the daily maintenance dose. Children under 4 years of age received half this amount. In vitro sensitivity tests showed that 75.4% of the organisms cultured were sensitive to sulfadimethoxine and 24.6% were resistant. The clinical response was excellent to good in 94 patients (88.7%) and poor in 12 patients (11.3%); in the former, improvement was noted within 24 hours after administration of the drug. Only one patient had side-reactions to sulfadimethoxine therapy, and these were mild and disappeared when the drug was withdrawn. From the results presented here, I feel that sulfadimethoxine is a drug of first choice for acute respiratory conditions. Also, it should be excellent for prophylactic use in chronic lung conditions (i. e., pulmonary emphysema, bronchiectasis, and chronic bronchitis). Further investigation and detailed clinical study of its uses in the latter conditions are warranted.

1924 Broadway.

Madribon for this clinical study was supplied by Hoffman-La Roche, Inc., Nutley, N. J.

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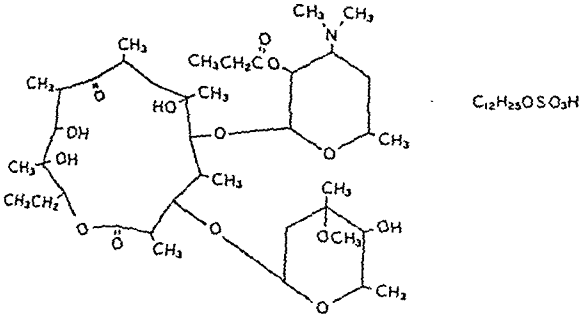
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. Kautz, M.D., *Secretary.*

Erythromycin Propionate Lauryl Sulfate (Ilosone).—Propionyl Erythromycin Ester Lauryl Sulfate.—The lauryl sulfate salt of the propionic acid ester of erythromycin.—The structural formula of erythromycin propionate lauryl sulfate may be represented as follows:



Actions and Uses.—Erythromycin propionate lauryl sulfate has the same uses as erythromycin free base, erythromycin propionate, and other orally administered esters of this antibiotic. Accordingly, it is indicated in the treatment of erythromycin-susceptible infections which are suitable for orally administered antibiotic therapy. The lauryl sulfate salt of erythromycin propionate has an advantage over both the propionate ester and erythromycin base since it is acid stable and, thus, is capable of producing therapeutic blood levels, when given with food, that are at least equal to those obtained when given to fasting patients. Erythromycin propionate lauryl sulfate is also more palatable in suspension than erythromycin propionate itself. Studies in test subjects have shown that the lauryl sulfate ion does not appear in the blood or urine and that the drug appears in the blood as erythromycin free base and erythromycin propionate. Although probably not specifically associated with the administration of the lauryl sulfate form of the drug, soft stools, nausea, and vomiting have been observed as occasional side-effects.

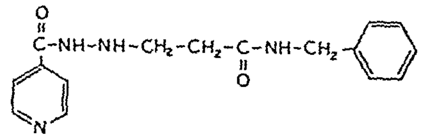
Dosage.—Erythromycin propionate lauryl sulfate is administered orally and is apparently equally well absorbed when given in the fasting state or in conjunction with food. Dosage is expressed in terms of the free base. The usual dosage for adults with moderate infections is 250 mg. every six hours; for more severe infections the dosage is 500 mg. every six hours. In overwhelming erythromycin-susceptible infections which require 1 Gm. or more at six-hour intervals, consideration should be given to the use of a parenteral form of the drug. In children with moderate infections, the dosage for infants weighing up to 25 lb. (11.3 kg.) is 5 mg. per pound of body weight given every six hours; for children weighing up to 50 lb. (22.7 kg.), 125 mg. given every six hours; and for those who weigh 50 lb. and over, 250 mg. given every six hours. For severe infections in children, the dosage ranges from 20 to 40 mg. per pound of body weight per day given in divided amounts; the dosage used for adults may be used in children weighing over 50 lb.

Preparations.—capsules 125, 250 mg.; drops (oral) 100 mg. per cc.; suspension (oral) 25 mg. per cc.

Year of introduction: 1959.

Eli Lilly and Company cooperated by furnishing scientific data to aid in the evaluation of erythromycin propionate lauryl sulfate.

Nialamide (Niamid).—N-Benzyl-β(isonicotinoyl- [illegible] (2-[Benzylcarbamyl] [illegible].—The structural formula of nialamide may be represented as follows:



Actions and Uses.—Nialamide is a monoamine oxidase inhibitor used in the management of emotional and psychiatric disorders in which the predominant symptom is depression. The drug may thus be tried in such conditions as psychoneurotic and schizophrenic depressions, involutional melancholia, and manic-depressive reactions. A definitive appraisal of the value of nialamide in these conditions must await carefully planned and controlled comparative studies; early reports, based largely on subjective impressions, suggest that it has about the same degree of effectiveness as iproniazid and other monoamine oxidase inhibitors. Elevation of mood, increased physical activity and mental alertness, and improvement in appetite characterize favorable responses. A substantial number of patients with anergic schizophrenia show some degree of improvement, as measured by such criteria as increased activity, fewer bizarre mannerisms, participation in adjunctive therapy, accessibility, and interest in the environment. Although no drug presently available can be considered as effective or as reliable as electroshock in the management of serious depressions, drug therapy merits a trial in milder depressions in which electroshock is neither usual nor justifiable. Monoamine oxidase inhibitors may also be successful in some cases of depression not responding adequately to electroshock; used in conjunction with electroshock, they may reduce the number of shock treatments required. Therapeutic effects appear somewhat more rapidly with nialamide than with iproniazid; a few patients begin to show improvement within two or three days, and most patients within two weeks, after treatment is begun. Further study is necessary to determine the frequency with which relapse occurs after discontinuance of therapy.

Like other drugs used in the treatment of depression, nialamide is to be regarded as an adjunct to, rather than a replacement of, other measures, including psychotherapy, reduction of environmental stresses, and improvement of the social milieu. Because of its slow onset of action, it is of no value in the management of psychiatric emergencies. In patients with suicidal tendencies, a course of electroshock treatment should precede initiation of nialamide therapy. Nialamide cannot be relied on to control anxiety, agitation, or panic; therefore, in depressive states in which these symptoms are complicating factors, other drugs must often be given concomitantly.

Nialamide apparently reduces the frequency and severity of attacks of angina pectoris but is of no value in alleviating the pain of attacks when they occur. Patients should be warned against overexertion because nialamide has no effect on the pathological condition responsible for anginal attacks. It is also necessary to watch the blood pressure of patients treated with nialamide, although this drug seems to have less hypotensive effect than some monoamine oxidase inhibitors.

Side-Effects.—The most common side-effects of nialamide are nervousness, restlessness, and insomnia. Blurred vision, dizziness, dryness of the mouth, and increased sweating have also been reported. Hypotensive reactions are rare when nialamide is administered alone but are not uncommon when chlorothiazide or closely related drugs are given concomitantly. Patients with hypertension have manifested a transient moderate rise in blood pressure.

Hepatic damage, which has occurred with other monoamine oxidase inhibitors, has not yet been noted with nialamide; however, present experience is much too limited to justify the assumption that hepatic toxicity will not be encountered after the compound receives more extensive usage. It is suggested, therefore, that patients receiving the drug in large doses or over an extended time have periodic tests of hepatic function. Blood cell counts at regular intervals and careful observation for other signs of serious toxicity are also recommended. The drug should be given cautiously, if at all, to patients with serious renal or hepatic disease.

Other drugs must be administered with caution and, often in reduced doses, to the patient receiving nialamide. For example, nialamide has been shown to prolong the central depressant effects of hexobarbital and to augment the hypotensive effects of chlorothiazide. Theoretical considerations suggest that the action of amphetamine and other sympathomimetic amines might also be enhanced.

Pharmacology.—Nialamide, a potent inhibitor of monoamine oxidase in vitro, increases the concentrations of serotonin and norepinephrine in the brain stem in several species and antagonizes the depressant effects of reserpine. However, definite proof that its therapeutic effects in depressive illnesses are related to these actions is lacking. The mechanisms through which it exerts its apparent beneficial effects in angina pectoris are also unknown. Since electrocardiographic findings are not altered and since the incidence of acute coronary thrombosis in patients receiving the drug apparently is not reduced, it is assumed that there is no amelioration of the underlying pathology. Usual methods of testing do not reveal any significant analgesic properties.

After oral administration, plasma concentrations reach a peak in one-half to three hours and decline to very low levels within eight hours. Nialamide is largely excreted unchanged in the urine but is partly broken down to isonicotinic acid and two unidentified degradation products. Preliminary studies, based on the concentration of isonicotinic acid appearing in the urine, suggest that conversion of nialamide to free hydrazines is a less important path of metabolic degradation than for iproniazid.

Dosage.—Nialamide is administered orally. The dosage should be adjusted in accordance with the response of each patient. Since effects may be delayed, each dosage level should be continued for several days, unless untoward effects intervene, in order that an accurate estimate of the therapeutic response can be made.

The usual dose is 75 to 100 mg. per day, either as a single dose or in divided doses. This daily dose may be increased or decreased in accordance with tolerance and response.

After a satisfactory response is obtained, reduction in dosage is often possible. Maintenance doses as low as 12.5 mg. daily or on alternate days may be satisfactory.

Preparations.—tablets 25, 100 mg.

Year of introduction: 1959.

Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., cooperated by furnishing scientific data to aid in the evaluation of nialamide.

CLINICAL SCIENCE

CONTROVERSY IN IDIOPATHIC THROMBOCYTOPENIC PURPURA

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That the basic aspects of medicine—its chemistry, immunology, and genetics—should be becoming ever more complex is not difficult to understand. But that even relatively simple clinical decisions should have become matters for controversy is at first blush surprising. This has happened in the management of idiopathic thrombocytopenic purpura (ITP). Why it has happened, what are the controversial points, and how they can be resolved —these are the subjects of the present discussion.

When in 1916 Kaznelson [1] of Prague, cognizant of the rather dramatic effects of splenectomy in some cases of hemolytic anemia as described by Banti and Micheli in 1913-1915, suggested that the operation might be beneficial in Werlhof's disease, it was fortunate that in the first cases the operation was successful; in others, the results were far from encouraging. Nevertheless, news of this new mode of therapy for a previously intractable and at times serious disease spread rapidly, and, before long, splenectomy was universally accepted as the best and perhaps only definitive therapeutic procedure for the disease. In fact, some observers emphasized the urgent need for removing the spleen as soon as the diagnosis was made, particularly in the acute cases, and at least one group recommended emergency splenectomy for the acute hemorrhagic crisis.

Relation Between Etiology of ITP and Splenectomy

In the course of time, rumblings of doubt began to be heard: that neither the immediate nor the long-term results of splenectomy were by any means certain; that to perform an emergency splenectomy on a person bleeding actively from all the mucous membranes and into the skin was apt to be hazardous and not infrequently fatal; and that it might be better to operate on a person who was "quieter" and less likely to bleed.[2] Furthermore, since some cases of apparently typical ITP were due to use of drugs such as allyl-isopropyl-acetyl-carbamide (Sedormid) and quinidine, it surely was folly to urge splenectomy in such situations. It is clear that the accumulation of one bit of knowledge after another during the past decade has resulted in an almost complete revolution in concepts of the pathogenic mechanisms of the disease and its therapy. Inevitably, a certain amount of controversy has crept into this rapidly changing field whose contours have by no means jelled. This is particularly the case when it comes to therapy.

In 1951, Hirsch and I [3] pointed out that one could discriminate in ITP two main classes of cases: (1) acute and self-limited and (2) chronic. In the first type, the purpura came on acutely, "out of a clear sky" and without previous history; the bleeding from mucous membranes and into the skin was intense and often fulminating; the platelet count was exceedingly low; and the bone marrow megakaryocytes were usually normal in number. In a few days to one week, the hemorrhagic crisis subsided; after one month, a few months, or even longer in some cases the platelet count rose and gradually reached normal. Some of the cases appeared a week or two after an attack of chicken pox or measles; in others there was a history of either a recent virus infection, exposure to drugs or chemicals, or of an injection of one of the vaccines against poliomyelitis or influenza. In other cases, however, no antecedent etiological factor could be ascertained. It seemed likely that some sort of hypersensitivity phenomenon was present and that this had induced a sudden and transient reduction in the number of platelets. To perform splenectomy under these circumstances might introduce merely an incident in the course of a self-limited disease, and the supposed beneficial effect of that operation might well be a coincidence.

Effect of New Techniques on Therapy.—At about this time (1950-1951), the appearance on the scene of two "medical" measures made the difficult problem of "waiting out" a hemorrhagic crisis much easier. These were (1) the development of siliconized apparatus and later of the plastic bag for the collection and administration of fresh blood containing viable platelets [4]; and (2) the availability for clinical use of ACTH and the corticosteroids. With the first type of agent, it was now possible to raise the platelet count and even to perform major operations with relative impunity in patients with extremely low platelet counts. The steroid hormones seemed to have a real effect in reducing the bleeding tendency, even when the platelet count itself showed no tendency to rise.[5] With these two new arrows in the "quiver" of the therapeutic armament, it was possible to convert an extremely ill, dangerously bleeding patient, into a relatively healthy one within several hours. Splenectomy could then be

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decided on in a more leisurely fashion and under less tense circumstances.

Should splenectomy, then, be performed in the acute cases, perhaps after a few hours or days of waiting? Some authorities said "yes"; some "no." Some said that acute cases (other than those due to drugs) occurred only in childhood, as after an exanthem; that all the cases in adults were in reality chronic ones with an acute exacerbation. In these, it would be better to remove the spleen without further procrastination. On the other hand, we have observed many acute, self-limited, and non-drug-related cases in adults, who have either developed complete remissions with use of corticosteroids or have become completely well without therapy. If this is the case, why should the patient be subjected to the hazards of an operative procedure, particularly when this may be completely unnecessary?

The chronic cases represent a totally different situation; their history is a prolonged one; they have their "ups and downs": sometimes there is active bleeding, most of the time there is not. Menorrhagia is common; pigmentation of the legs develops because of the deposition of iron into the skin from the petechiae. The platelet count, although always low, may be one-third to one-half of normal; the bone marrow is crowded with megakaryocytes, but platelet production from them seems to be reduced. Originally, it was thought by some (e.g., Frank[6] and myself, among others) that a disturbance of the spleen was responsible for the disorder, possibly through the elaboration of a "humor" of some sort which acted on the megakaryocytes of the marrow to prevent the production of platelets. To remove the spleen would be to remove the site of production of the abnormal factor, and thus allow normal thrombocytopoiesis. Since bone marrow studies revealed abundant megakaryocytes with but little platelet production before splenectomy and abundant megakaryocytes with striking platelet production after splenectomy, it seemed natural to conclude that a form of hypersplenism was involved.[7] However, in 1951, Evans and associates[8] pointed out several analogies between autoimmune hemolytic anemia and ITP and in addition they found platelet agglutinins in some cases of the latter disorder. The suggestion that ITP might be an immunologic disease was further advanced in the studies of Harrington and associates[9] and Stefanini and associates.[10] Ample demonstration was made that a thrombocytopenic factor was present in the blood and that this was probably immunologic in character. Platelet agglutinins, apparently autoantibody in type, were found consistently by some observers, inconsistently by others.[11]

Effect of New Immunologic Concept of ITP on Therapy

These observations, and many others, did much to alter thinking regarding pathogenic mechanisms and therapy. Since ITP might be an autoimmune disorder, it might also, like autoimmune hemolytic anemia, be permanently so, i.e., "self-perpetuating." Therefore, what could splenectomy accomplish? The spleen could, of course, be an important site for antibody production and could simultaneously remove platelets injured by antibody. With removal of the spleen, injured platelets might well have a normal survival time. That this was apparently the case was indicated by the demonstration of "thrombocytopenic factor" in some splenectomized patients, and by the fact that some babies born of splenectomized mothers (in remission) could still be thrombocytopenic.[11b] On the other hand, in other cases, splenectomy had no such effect on the blood platelet level. Our own statistics indicated (in 1951) that the operation was without effect in about one-third of the cases; by 1960, it was evident that only about one-half of patients with chronic cases were benefited by splenectomy. Indications pointed to the immunologic abnormality as the fundamental one, with the splenic function secondary. Thus, even in the chronic cases the value of splenectomy seemed to be downgraded.

Harrington and associates[11b] emphasized not only the immunologic concept, but the importance of the demonstration of platelet agglutinins in ITP and their relation to therapy. They found platelet agglutinins in about 70% of the cases; the incidence of antibody detection was not influenced by sex, age, or duration of the disease. Whether splenectomy should be performed was apparently largely determined by the presence or absence of these elusive proteins; if present, splenectomy was carried out. On the other hand, most observers throughout the world have concluded that the agglutination of platelets by a serologic factor may be quite nonspecific and that the finding of platelet agglutinins, except in conjunction with drug (e.g., allyl-isopropyl-acetylcarbamide and quinidine) hypersensitivity, should be considered suspect (i.e., nonspecific agglutination and other nonimmunologic factors). It has been my impression that to base the decision to perform a serious operation such as splenectomy on the presence or absence of such a doubtful entity (or doubtfully determined entity) as a platelet agglutinating factor in the serum is a rather questionable practice.

The value of splenectomy was reduced further by the knowledge that the platelet count in patients with acute and chronic cases, and even in relapsed splenectomized patients, could be brought to normal by the use of large doses of various corticosteroids in about three-quarters of the cases, the percentage being at least 80 in the acute cases and about 60 in the chronic ones. Whether this rise of the platelet count to normal values can be maintained in the chronic cases is another matter; often it can not, except by dint of the continued use of large doses of such materials as prednisone and dexamethasone. The desirability of long-term steroid therapy is, of course, questionable. On the other hand, many of the chronic cases, once their platelet counts have reached normal values, can be maintained on doses of prednisone varying from 2.5 to 10.0 mg. daily. To be sure, the platelet count might then be only one-third or one-half of normal in some cases, but at this level hemorrhagic symptoms were no longer present. Parenthetically, it should be mentioned that there often is altogether too much concern with a number, i.e., a supposedly normal number of platelets, or of red blood cells, or of leukocytes. The physician feels that he must get the number just right. Actually, with one-third to one-half the normal number of platelets, hemorrhagic manifestations are hardly ever present, and the patient can carry on his usual activities without difficulty. Operative intervention may even be possible under these circumstances, but assistance from platelet transfusions and corticosteroids may be advisable. This has posed a problem—why remove the spleen in a healthy person, whose only abnormality is a slight to moderate reduction in platelet count, which has but little, if any, effect on the coagulation mechanism? We have observed such patients year after year without hemorrhagic manifestations and without complications from long-term steroid therapy.

It is futhermore becoming increasingly apparent that systemic lupus erythematosus (SLE) and ITP are closely related, at least in some cases. Thus, some patients with apparently typical ITP develop systemic SLE after splenectomy. Other patients with ITP develop autoimmune hemolytic anemia and eventually SLE. We have concluded that ITP is in some cases one of the many immunologic manifestations of the larger disease and not infrequently a "prodrome" of SLE.[12] If this be the case, and if—as some of our observations suggest—removal of the spleen may in some way result in dissemination of previously occult lupus, this would again diminish one's enthusiasm for routine splenectomy in patients with ITP.

Thus, the controversial points in ITP, to be discussed in detail below, can be defined as follows: 1. Are there acute and self-limited as well as chronic cases? 2. Should splenectomy be performed in a patient with acute, fulminating ITP? 3. What is the place of corticosteroid therapy in chronic ITP? What is the place of splenectomy? 4. What is the significance of the platelet agglutinin demonstration in ITP? 5. Is ITP really a "prodrome" of SLE in many cases, and does splenectomy actually help disseminate a previously latent lupus?

Controversial Aspects

Discrimination Between Acute and Chronic Cases.—Admittedly, it is difficult to distinguish between acute and chronic cases of ITP. A chronic case may have been quiescent for years and then have flared up with an acute exacerbation. A patient with an apparently typical acute case may present a history of ecchymoses of years' duration, whose significance is uncertain. Is the acute case perhaps due to exposure to a drug or a chemical? How does one know whether this is truly acute and self-limited and not the beginning of a chronic situation? (About 20% of apparently typical cases of acute ITP become chronic.) Although these questions are all difficult to answer, particularly in some cases, it is possible in most instances to discriminate readily between the acute and chronic examples. Careful history-taking is essential, with particular reference to recent infections, use of antibiotics, exposure to chemicals and drugs, and administration of potent vaccines as for poliomyelitis and Asian influenza. To be sure, the finding of a possible etiological agent may be coincidental rather than of any real pathogenic importance, but a search must nevertheless be made.

Contraindications to Splenectomy in Acute ITP.—"Emergency" removal of the spleen in an acute hemorrhagic crisis (in either an acute or a chronic case) seems contraindicated for the following reasons: A striking improvement in the situation may be obtained with the use of large doses of corticosteroids (50-100 mg. of prednisone) and of fresh plastic bag blood. These measures have, in my experience, been sufficient to control bleeding, and I have seen no examples of cerebral hemorrhage in the past five years. Splenectomy can be decided on at leisure. My own inclination is to keep the latter question open for at least four to six months, perhaps longer. In children, the time can be stretched out even further, for at least one year. The control of a person with a low platelet level but without much tendency to bleed is relatively easy and can often be achieved with administration of even conventional doses of steroids (e.g., prednisone 25 to 40 mg. per day initially). If the platelet count then rises to normal in a month or two, much has been gained, namely, (1) performance of an operation under difficult circumstances has been avoided and (2) a self-limited course may have been exposed. If the platelet count has not returned to normal, larger doses of corticosteroids can be tried before splenectomy is seriously considered. If a response occurs, all is well; maintenance therapy can be used for a lengthy period and the matter of splenectomy decided on at leisure. If a relapse occurs, one is evidently dealing with a chronic case.

Management of the Chronic Case.—If one has decided that the case is a chronic one, should splenectomy be carried out forthwith? This was at one time our recommendation, but now one hesitates. A trial of corticosteroids in large doses is in order in the attempt to bring the platelet count to normal. After one to three weeks of therapy with large doses, the corticosteroids are gradually reduced to maintenance levels (5 to 15 mg. of prednisone daily). The initial dose of prednisone in most adult patients is 50 to 100 mg. daily; it was found by trial and error that "conventional" doses of the corticosteroids were not enough in many cases. An analogous situation is found in autoimmune hemolytic anemia, in which the correct dose is the "adequate" dose. If the platelets remain at reasonable levels (one-third to one-half of normal) and there is no undue bleeding, splenectomy is certainly not urgently required, and in fact can be postponed indefinitely. If more than 10 mg. per day of prednisone are required, this introduces the definite possibility that the various complications of prolonged steroid therapy may ensue. After 6 to 18 months of therapeutic trial and error, one can then recommend splenectomy for patients with refractory cases. This is a moderate position, allowing the patient every possibility of remission without surgical intervention and yet not ruling out splenectomy altogether. If splenectomy is decided on, the question whether SLE will develop is a purely academic one. The close relationship of that disease with ITP cannot be denied; that it should be a deterrent to splenectomy, once operation has been decided on, is questionable. It should be a restraining factor, however, in making a quick decision.

This regimen for the therapy of chronic ITP has been termed a "challenge" to splenectomy [13]; it is by no means so. Rather, it is a "challenge" to the ready acceptance of splenectomy as the only definitive therapy for ITP and to the performance of the operation in a routine manner once the diagnosis has been made. To be sure, recent statistics from Wintrobe's clinic are cited to show that splenectomy was successful in 81% of cases of ITP, whereas corticosteroid therapy was successful in only 38%.[13] (Ten of eighteen cases in the series of Carpenter and associates [13] responded to prednisone in maximal doses of 40 mg. daily. It should be realized that a failure of response to corticosteroids may be a result of inadequate dosage. In any event, it is obvious from the paper by Carpenter and associates that (1) a waiting period, even up to one year, is desirable, especially in the young—since complete remissions may appear spontaneously, and (2) the corticosteroids, even in relatively small doses, may induce full remissions in a goodly proportion of cases. Thus, reading between the lines, management of these cases in Wintrobe's clinic appears to be much as in the New England Center Hospital: splenectomy is by no means an emergency procedure and there is a sufficient waiting period, even up to one year, to assess the question of spontaneous remission.

Role of Platelet Agglutinins in Determining Splenectomy.—The status of the platelet "agglutinins" and of the technical determination of platelet agglutinins must be considered uncertain. Do platelets become agglutinated in vitro for nonspecific reasons, such as the glassware used in manipulations? Does the agglutination of platelets in a serum-platelet mixture actually indicate the presence of platelet agglutinins? Are there really platelet agglutinins? These questions may be answered either negatively or affirmatively, depending on the experience which has been amassed in different clinics. That there is a thrombocytopenic factor in ITP, that ITP is in most cases an immunologic disorder, and that actual antibodies against platelets can be demonstrated in various ways in purpuras due to allyl-isopropyl-acetylcarbamide, quinidine, and other drugs [14]—these are relatively unquestioned. That platelet agglutinins are almost routinely and readily found in ITP and that their presence is meaningful—these are the subjects of considerable controversy. Many attempts have been made to improve and elaborate new techniques for demonstrating platelet agglutinins, but it is questionable at this time whether they have contributed much to the solution of this problem. Under these circumstances, it would seem inadvisable to decide on such a serious matter as splenectomy merely from the results of a platelet agglutinin determination.

Relationships Between ITP and SLE, and Apparent Dissemination of SLE after Splenectomy for ITP.—There are many indications that ITP and SLE are more closely related than seemed apparent some years ago: apparently typical cases of ITP may either show the histological indications of lupus at splenectomy [15] or be followed by the characteristic features of the disease at some time in the future. Typical cases of SLE may show the characteristic features of ITP at some time in their course; patients with apparently typical examples of ITP may develop other autoimmune disturbances such as hemolytic anemia or a positive serologic test for syphilis—and later the characteristic features of lupus may appear. About 9 of 10 cases of SLE occur in young women; a somewhat similar ratio of women to men occurs among patients with chronic ITP. We consider every patient with ITP as an SLE "suspect"; a follow-up study of splenectomized patients with ITP led to the uncovering of a number of hitherto unsuspected examples of SLE. Of 51 splenectomized patients, 8 later developed definite SLE and 2 more had probable examples of that disorder, i.e., 19.6% had either definite or probable examples.[16]

As for dissemination of latent SLE by splenectomy, this may have happened in several of our patients and we have had many personal communications indicating that our observations are by no means isolated phenomena. The possibility is present that the removal of the spleen may in some manner modify immunologic behavior within the body, thus leading to the sudden activity of various previously latent immunologic sites.[17] That ITP may be only one immunologic manifestation, among many, of SLE is of considerable interest with reference to the nature of that disease, which I have recently likened to the experimentally induced runt disease in animals.[18] That splenectomy may conceivably disseminate a latent example of SLE is of considerable practical importance, since one would not wish to aggravate a previously mild, even occult disorder and bring to the fore a potentially fatal disease. This should make one think at least twice before finally deciding on splenectomy in a young woman with chronic ITP.

Comment.—In view of the foregoing, should splenectomy be emphasized as the chief mode of therapy in the present stage of our more or less imperfect knowledge of ITP? It is my contention that ITP is either an acute, self-limited condition, in which case it should be allowed sufficient time to demonstrate its self-limited character without splenectomy, or a chronic, "self-perpetuating" immune state, in which case the benefits of splenectomy are questionable. To be sure, removal of the spleen may remove an organ which tends to sequester immune body-coated platelets, or perhaps allow platelet production from the megakaryocytes to proceed normally, as was my original contention. The results of splenectomy being uncertain, however, a trial of either "skillful neglect" or of the use of corticosteroids should be made. Although adequate, often large, doses of steroids will raise the platelet count to normal in most chronic cases, the main question revolves about whether small maintenance doses will maintain the platelets at nonhemorrhagic levels. The continuance of therapy with large doses of corticosteroids over a lengthy period is certainly unjustified. Since in about one-third of the chronic cases reasonably good platelet levels can be maintained indefinitely (after "loading" therapy) with a dosage level of prednisone of 5 mg. daily, this, or no treatment, seems more justifiable than splenectomy in many cases. In any event, this therapeutic principle should be investigated before splenectomy is finally done as a measure of last resort.

Summary and Conclusions

As can be seen from the above, the therapeutic management of idiopathic thrombocytopenic purpura (ITP) is by no means as clearcut as it seemed to be a decade ago, when splenectomy was the only therapeutic procedure which had any well-defined effect on the platelet count. Now that more is known of the disease—its probable autoimmune character and its not infrequent relationship to systemic lupus erythematosis (SLE)—and now that other therapeutic principles are available, including administration of fresh platelets and of corticosteroids in large dosage, the question of which method of treatment is desirable in a given patient, at a given moment, has become a matter of considerable concern and discussion. To be sure, the many new findings that have been made in ITP in the last decade have clarified many facets of this protean disease. Unfortunately, these new developments have often made the task of management of the disease difficult and controversial. Thus, it can no longer be said that splenectomy is the only definitive therapeutic procedure. With the availability of corticosteroids, fresh platelets, and above all patience one can now afford the luxury of pro and con discussion regarding one or another therapeutic method. Certainly, the urgency for carrying out splenectomy in a given case of ITP has dwindled considerably in the past decade. Perhaps future developments will some day make this operative measure altogether archaic.

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THE JOURNAL
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CHICKENPOX AND PREGNANCY

IN 1942, Waring, Neuberger, and Geever reported the first well-documented case of fatal chickenpox in an adult. Subsequently, numerous other instances have been described, but it is still not fully realized that this relatively benign childhood disease is of such a potentially disastrous nature in adults.

In this issue of The Journal, p. 978, Fish reports four maternal deaths due to chickenpox, which reemphasizes the fact that this virus disease, as many others, may have an entirely different host reaction in adults as compared to children. In none of the cases was the seriousness of the patient's condition realized by the attending physician until marked pulmonary distress occurred. This was probably due to a lack of awareness that chickenpox can produce severe interstitial pneumonitis and other significant visceral complications. Although these cases were concurrent with pregnancy, there is apparently no particular susceptibility to varicella during gestation nor any increased danger of dissemination.

Varicella pneumonitis is rarely, if ever, seen in children and is probably not very common in adults; otherwise it would be more frequently reported. Perhaps many mild cases go unrecognized. However, the potential danger of this condition cannot be ignored, and any adult who develops chickenpox should be carefully observed for evidence of pulmonary involvement or other signs of dissemination.

The question arises as to whether any preventive measures should be taken when an adult, particularly a pregnant woman, is exposed to chickenpox. Since the effectiveness of gamma globulin and varicella immune serum is uncertain in attenuating or preventing infection, and since there is no definite evidence that danger exists to the actual developmental process in the fetus, it is probably unnecessary to resort to any special measures in an attempt to prevent or modify the infection.

In women who actually develop chickenpox during pregnancy, it is suggested that exceptionally close attention be paid to the clinical course of the disease and the patient hospitalized immediately if any sign of pulmonary or other systemic involvement occurs. There is no specific drug therapy available for disseminated varicella; it has been shown that antibiotics have no great beneficial effect except perhaps to decrease the amount of secondary infection. The management of the pulmonary and visceral complications of chickenpox should be directed toward correcting the abnormalities of function for a sufficient period of time to allow the disease to complete its course and for recovery to occur.

Occasionally, infants will be born with chickenpox when the mother is suffering from this disease. Although congenital varicella is uncommon, this eventuality should be considered in any pregnant woman near term who develops chickenpox.

COVER—1960 DESIGN

The façade of this issue of The Journal has been selected among several suggestions that were scrutinized with a critical eye in recent months. For many years the cover was a one-color product, and the table of contents shared space with advertising. The introduction of a smattering of red and the increase in the Editorial-Advertising ratio occurred several years ago. Since early Spring the tempo of change has been augmented significantly. The omission of advertising on the April 23rd cover of The Journal was the initial presentation to the medical profession of the philosophy of the current regimen for Improvement of the Scientific Publications of the A. M. A. It is reassuring to recount that this phase brought forth no hurricane of protestations. The comments sent on to this office were favorable. As the weeks went along, minor modifications here and little changes there were introduced slyly. More "white space" appeared; the black lettering did not monopolize the cover. Ellipses and the unofficial seal of the A. M. A. were eliminated. These omissions prompted a few queries from members. Prior to and including this phase of metamorphosis, approval by the Board of Trustees was not necessary. Before taking the final step, however, the Board was taken into confidence for official approval.

A number of suggestions for a new cover were prepared, reviewed, and rejected during the intervening weeks. Some of the modifications were submitted by members of the Editorial Division; in other instances, experts in periodical cover design offered consultant counsel. The charge to either group was identical: "Please modify the cover to make it as attractive as possible but under no circumstances destroy the basic traditional design!" The distinguished identity of The Journal should not be discarded. The cover of this issue was the unanimous selection by the members of the Division of Scientific Publications and the representatives of the office of the Executive Vice President. Lastly, approval by the Board of Trustees on June 11, 1960, clinched the firm commitment within the Association.

The Journal remains The Journal of the American Medical Association. J. A. M. A. is not a new name for the official publication of this body. It is urged that Librarians receive this new cover without alarm. The cover—1960 Design, involves no basic change in cataloging. The position of The Journal of the American Medical Association in the listing of medical journals remains, as well as its stature among medical periodicals in the free world.

J. H. T.

ABSORPTION OF VITAMIN B_{12}

In pernicious anemia, the failure of transport of 1 mcg. of vitamin B_{12} daily across the mucosa of the whole length of the small intestine leads to a deficiency which, unless effectively treated, is lethal. This failure is due to absence in the gastric secretion of intrinsic factor (IF), which is not known to have any other function than the facilitation of transmucosal transfer of vitamin B_{12}. Although the broad outlines of the vitamin B_{12}-IF relationship are fairly clear, a full understanding of the mechanisms involved is wanting. The use of vitamin B_{12} labeled with radioactive cobalt has helped greatly to clarify the picture, but the forms in which vitamin B_{12} exists in foods and the tissues of the body, the identity of IF, and the precise nature of the vitamin B_{12}-IF complex remain to be established. Dialysis experiments have shown that normal gastric juice can remove vitamin B_{12} from muscle and casein[1]; such a process may well be an essential first step in vitamin B_{12} absorption from food substances, but the effectiveness of raw liver in pernicious anemia, in which case this action of gastric juice is presumably absent, can only be explained in terms of some of the vitamin in the liver's being freely available for absorption. It is known that a significant fraction of a large oral dose of the pure vitamin is absorbed in the absence of IF, although the absorption pattern is different from that mediated by IF, and liver vitamin B_{12} may be absorbed by the same mechanism. It has been postulated, however, that vitamin B_{12} in liver is present in part in a form which behaves like a vitamin B_{12}-IF complex; conclusive evidence for this is lacking.

Binding of vitamin B_{12} to make it nondialyzable and unavailable to micro-organisms[2] is a property not only of all preparations of IF but also of some other substances which have no IF activity. Until pure IF is isolated, it will not be known if it binds vitamin B_{12} in these ways; certainly vitamin B_{12} bound to gastric juice is preferentially absorbed.[3]

Observations in man and in animals suggest that the site of vitamin B_{12} absorption is the middle and lower part of the small intestine. The mechanisms involved here have been studied, with use of loops of rat intestine with an intact circulation, segments of isolated rat intestine, and liver slices, which behave in some ways similarly to intestinal mucosa.

Uptake of vitamin B_{12} by these tissues in vitro requires the presence of calcium ions. A chelating agent, ethylenediamine tetra-acetate (EDTA), inhibits this uptake and inhibits absorption of vitamin B_{12} in man. Failure of vitamin B_{12} absorption in some cases of steatorrhea may be due to the absence of calcium ion in the intestinal contents. This Ca^{++}-dependent mucosal binding is not to be equated with absorption, however, because it occurs in the rat with both homologous and heterologous IF preparations, whereas the heterologous preparations used in these experiments do not restore absorption of vitamin B_{12} in gastrectomized rats.

Vitamin B_{12}, once bound to the intestinal mucosa, does not depend on Ca^{++} for its continued binding[1] when a homologous IF preparation is used and washing with EDTA does not remove the vitamin, but such treatment removes bound vitamin B_{12} when heterologous IF is used. It is possible that absorbable vitamin B_{12} bound to the intestinal mucosa is quickly released from the Ca^{++}-dependent bond and is thus able to proceed a further step to proper absorption, whereas nonabsorbable vitamin B_{12}, in complex with heterologous IF, is not freed from the Ca^{++}-dependent bond. Recently, it has been shown[1] that there is release of the vitamin bound to rat IF on incubation with rat intestine and that this occurs less readily, or not at all, when the vitamin is bound to heterologous IF. Such a release mechanism may well determine the absorption of vitamin B_{12} in the intact intestine. Until pure IF is isolated, free of all "inhibitory" contaminants, the evidence can only be taken as suggestive, heuristic, and not conclusive.

THE BOSS OF THE SHOP

The delivery of the J. A. M. A. to your office by a representative of the Postmaster General is the last step in a large number that occurs 52 or 53 times each year. The steps that precede deposition on your desk began at 535 North Dearborn Street with the receipt by the Division of Scientific Publications of the A. M. A. of a manuscript, an obituary notice, a news item or one of several other documents. The majority of decisions that concern acceptance or rejection and subsequent processing of the typewritten manuscripts are the responsibility of physicians in the Editorial Division.

Non-medical personnel have responsibilities also in the chain of publication. Robert Mayo, an alumnus of the Medill School of Journalism of Northwestern University and former editor of several magazines, is the most recent addition to the non-medical coterie. His name has appeared on the masthead in recent issues as Managing Editor. The publication of The Journal, the largest medical periodical in the free world, is a major undertaking and demands talent, experience and imagination, not only in the unbiased selection of scientific contributions but in the assurance that the communications selected will be processed promptly and will be available to the physician for perusal in a format attractive either for careful reading or casual scanning.

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The management of a manuscript that has been accepted for publication, in keeping with the contemporary philosophy in the Editorial Division, entails a minimum of "manuscript editing." There is no desire on my part to process a manuscript through a mental machine in order to conform to an established pattern or prototype. In the days gone by when I was on the dispatching end, it was my fervent wish that my style, inadequate though it was, would not be eliminated by the blue pencil of a conformist. Now that my position is altered, I sense the same feeling of compassion for the composer. A physician's style and word composition reflect his personality. I believe that it should not be altered any more than the photographer is entitled to alter a studio portrait. Not many of us will be photographed by Karsh, but each is entitled to retain his own portrait of composition. The conversion to the current policy has not been an easy one to promulgate. Furthermore, it is not accomplished in the entirety as of this date nor have the gains been achieved with complete equanimity. It should be appreciated, however, that this is the goal and every effort will be expended to reach it. The maturation of the galley proofs and subsequent make-up of each issue entail many additional steps best supervised by a managing editor who has had formal training and experience in publishing. Robert Mayo is the man. He is the boss of the shop.

But there is yet one other phase in the preparation of The Journal that seems indispensable to modern medical publications, except for those unique periodicals that survive without benefit of advertising. Immediately prior to my move to Chicago a clear separation of the responsibilities for the editorial and advertising pages was decreed by the Board of Trustees of the A. M. A. The Editorial Division has no claim upon advertising accepted since this decree; conversely, the department in the Business Division of the A. M. A. charged with acceptance of advertising has no preferred claims on the Editorial Division regarding acceptance of manuscripts for publication. Such a mandate is believed to be as important to medical publishing as was the separation of the church and state to Renaissance civilization. In order that such separation achieve the greatest good, Standards for Acceptance of Advertising by the scientific publications of the A. M. A. were prepared early this year. They appeared in The Journal (Jan. 30, 1960). It is my considered judgment that the current standards accomplish much in promoting better advertising of medicinal products.

The printing of The Journal, one of the last actions each week, was carried out at 535 North Dearborn Street until four years ago. Since that time the J. A. M. A. shares the McCall presses at Dayton, Ohio, with *Reader's Digest*, *Newsweek*, *Outdoor Life*, the *Harvard Business Review* and other publications that are distributed throughout the world. The return of the galley proofs to the Editorial Division and simultaneously to the authors and the correlation, subsequently, of the corrections portend completion. Make-up day is Tuesday. Selection of galleys of proper length to fit the several sections in the 150 pages each week, with the addition of fillers, occasionally, is a major assignment. These and many others are the duties of the new Managing Editor.

J. H. T.

USE OF AIR PRESSURE TO SPEED UP BLOOD TRANSFUSION

In acute hemorrhage it is sometimes necessary to transfuse blood very rapidly in order to save the patient's life. This can be done safely by a number of methods, such as inserting needles into more than one vein and thus running multiple infusions simultaneously; by using a large-bore needle for the venipuncture; by elevating the bottle to increase the hydrostatic pressure; or by connecting a three-way stopcock between the needle and the intravenous tubing, and pumping the blood in by syringe. Collection of blood from donors into plastic bags also makes possible rapid administration by direct pressure on the bag without any danger to the recipient. Whatever method is used, it is well to bear in mind that 10 cc. of 10% calcium gluconate should be injected intravenously for every 1,000 cc. of blood infused, in order to counteract the effect of the citrate in binding the ionized calcium.

Some workers have pumped air under pressure into the blood reservoir in order to speed up the blood transfusion. In a report of the Committee on Medicolegal Problems published in 1953,[1] it is pointed out that this method of transfusion has caused a number of deaths from air embolism, and that such accidents are inevitable when this method is used, unless a qualified transfusionist is constantly in attendance and vigilant during the procedure, in order to terminate it before air has a chance to enter the vein. Since this method is not foolproof and safe methods are available, the Committee maintained that blood transfusion under air pressure is to be condemned. Furthermore, the Committee warned that the transfusionist must bear in mind that air embolism as the cause of a patient's death after a blood transfusion may be considered *prima* facie evidence of negligence. The report by Reusch, Miyatake, and Ballinger[2] is therefore very disturbing; they describe four patients who sustained air embolism after blood transfusion, three of whom died.

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[1] Wiener, A. S.: Medicolegal Aspects of Blood Transfusion, Committee on Medicolegal Problems, J. A. M. A. **151**:1435-1443 (April 18) 1953.

[2] Ruesch, M.; Miyatake, S.; and Ballinger, C. M.: Continuing Hazard of Air Embolism During Pressure Transfusions, J. A. M. A. **172**:1476-1482 (April 2) 1960.

If the comments made in this recent report are true, namely, that transfusion of blood under air pressure is still in common use throughout the country, despite the report of the Committee on Medicolegal Problems, then their conclusion that there may be many unnecessary deaths from this cause every year is probably correct. Since transfusion of blood under air pressure is both unnecessary and dangerous, the time has come to prohibit the use of this method of transfusion by appropriate laws in our Sanitary Codes.

BOLIVIAN MEDICINE

The several countries of South America that border on the Atlantic, Pacific, or Caribbean waters are better known to North Americans than the two landlocked countries in the interior. Until a generation ago commercial and cultural exchange with South America was carried out principally by sea, and the inland countries were inaccessible and isolated. Progress, as measured by North American standards, was laggard, and natural resources in great variety were meager. Bolivia and Paraguay are the two countries in the Southern Hemisphere in this category. They have shared less in the advances of the 20th century than the majority of the other countries of the land to the south.[1] An occasional American has visited Bolivia for business purposes. A few Europeans, mainly Germans and English, have settled in Bolivia for the same purpose. La Paz, the capital, is the highest in the world. It lies almost 12,000 feet above sea level, somewhat higher than Lhasa, the capital of Tibet. Tin has been the principal natural product for generations. Few persons know little more than this about a country larger than the state of Texas, a standard of reference per se, with a population less than one-half that of the once largest state in the Union.

I would presume that some physicians have written about medical practice in the highlands of Bolivia. After a brief sojourn in this little-known country in the 1930's, I have eagerly sought books and communications that might bring me up to date on the subject. None has been discovered or brought to my attention until the publication recently of a vivid tale by a Viennese doctor practicing medicine in the jungle of northeastern Bolivia. In the perusal of the indoctrination pages of "Doctor in Bolivia,"[2] I was fearful lest the tale be as grisly as that told by Leonard Clark of his experiences in the jungles of Ecuador and Peru which border on the north.[3] Mautner was discreet in his selection of professional experiences, frank in his recounting of love and emotion ("At night all cats are grey . . ."), and skilled in his English composition. Mautner migrated to Bolivia as a victim of Naziism. His adopted country assigned him the position of health officer in a remote primitive village and allowed him the privilege of practicing medicine and dispensing drugs. Cows and oxen were the usual professional fees. Mud huts were the only homes. The doctor's office and home also was a mud hut with a dirt floor. The only running water came from a pitcher, not a tap. Hot water was available only after preparation in a kettle over an open fire. The other vessels were halves of shells from coconut-like fruit. Local anesthesia was induced by administering novocain dissolved in freshly boiled water. Sulfa drugs were the only antibiotics available at that time. Towels for drapes were not sterilized, they were freshly washed. Surgical gowns were not worn. Intravenous saline solution was manufactured on the spot from salt and boiled water. The surgical assistant was a friend, completely lacking in professional training. Major surgery was performed in native huts. Drip ether was the only general anesthetic available. Tuberculosis, syphilis, and malaria were common medical maladies. Crocodiles, snakes, and tigers were the hazards of the wild life. The primitive medicine men, *curanderos,* were the professional enemies.

Culture was almost nonexistent. Newspapers were flown in by plane every four or six weeks. Newspapers were so valuable that their use in outhouses was contrary to local custom. High blood pressure and duodenal ulcer were not observed. Aguardiente, 100-proof raw alcohol fermented from sugar cane, and Chicha, a beer-like liquid made from corn, were the only alcoholic drinks, usually homemade. They have been standard items for Bacchanalia in South America for centuries.

The two years of jungle practice undoubtedly were more rewarding philosophically and spiritually, than they were professionally, to the physician. The practice of medicine, in whatever area of the world, cannot be rewarding professionally without a few accoutrements of sanitation, modern medicines, and some professional assistance. Possibly the lack of these fundamental items caused Dr. Mautner to seek permission to come to the United States. Currently he is Director of Physical Medicine at Maimonides Hospital, Brooklyn, N. Y.

This story of life in the Bolivian jungle is expertly told. It moves swiftly, due to the fine style, and avoids any exaggeration or fabrication of jungle living or jungle practice.

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1. Hanson, E. P.: New World Guides to Latin American Republics, vol. 2, Andes and West Coast Countries, New York, Duell, Sloan & Pearce, Inc., 1950.

2. Mautner, H. E.: Doctor In Bolivia, Philadelphia, Chilton Co., Book Division, 1960.

3. Clark, L.: The Rivers Ran East, New York, Funk & Wagnalls Co., 1953.

GOVERNMENT SERVICES

AIR FORCE

Personal.—Brig. Gen Major Samuel White, command surgeon air training command, Randolph Air Force Base, Texas, was promoted to major general. General White has been air training command surgeon since May, 1959. He was transferred to ATC headquarters from Washington, D. C., where he was director of medical staffing and education, office of the surgeon general, United States Air Force.

ARMY

New Developments.—Medical aid men of the U. S. Army Combat Development Experimentation Center have tested infrared binoculars attached to their helmets. Using an infrared light source to bathe the battle area, the aid men can locate casualties quickly, without being detected by the enemy themselves. Locating, rendering first aid, and evacuating wounded from a combat area during hours of darkness has long been a serious problem.

Prevention of sepsis in battle wounds has been another vexing problem. During World War II and the Korean conflict, instruments were sterilized in steam sterilizers using a fuel source of liquid gasoline stored in pressure tanks. These required constant pumping, were difficult to transport, and on many occasions, proved dangerous due to their tendency to explode. An autoclave may prove to be the answer to instrument sterilization under combat conditions. The stream container is serviced by a small tin of gasoline impregnated wax which creats intense heat, and can be moved and handled safely. During emergencies, when the wax has been expended, a highly absorbtive clay plug has been developed to furnish heat. Soaked in gasoline, the plug is placed in a tin, and provides adequate heat to operate the autoclave for a short period.

Beds occupied by battle casualties in field and evacuation hospitals have, in the past, been constructed of materials and in designs ranging from simple straw pallets, to cumbersome iron frames. A newly-developed hospital bed that consists of a lightweight metal frame and a canvas sling, is undergoing field trial. It weighs only 27 lb., is collapsible, does not require a mattress, is capable of supporting 1,000 lb., and may be dropped from an airplane. This bed has longer than average length legs which permit comfortable and efficient treatment of patients. Metal cross-bars are accessories to the unit, and clip to the sides where they are used to suspend plasma and other fluid containers.

PUBLIC HEALTH SERVICE

Public Health Conference.—The Fifth CDC Biennial Conference for Public Health Veterinarians and Teachers of Preventive Medicine will be held Sept. 12 to 17 at the new facilities of the U. S. Public Health Service's Communicable Disease Center in Atlanta, Ga. Epidemiology and the control of animal diseases pertinent to public health will be the theme of the program. The major portion of the program will be devoted to discussions of the more important diseases of animals transmissible to man. The meetings are open not only to public health veterinarians and teachers of veterinary preventive medicine but also to research workers in comparative medicine and other interested persons.

Infant Death Rates.—Progress in reducing the death rate of infants has been slowing down in recent years, according to a study by Dr. Iwao M. Moriyama of the National Office of Vital Statistics, published in *Public Health Reports.* Until recently, the rate decline in infant mortality had been relatively fast. From 1933 to 1949 infant mortality declined 4.3% a year. Since 1950 the rate of decline has averaged about 2% a year. After reaching an all-time low of 26.0 per 1,000 live births in 1956, the rate has been rising in a few states and declining more slowly in others. The estimated rate for the nation as a whole was 26.4 for 1959.

The leveling-off of the death rates applies to neonates as well as to infants between one month and one year old and is especially clear for cities of 25,000 and over. The same phenomenon is discernible also in data for Norway, Sweden, Denmark, the Netherlands, England, Wales, and Australia, although the turning point was reached a little later in these countries than in the United States. For nonwhite infants, a slowing down of the rate of decline for deaths from pneumonia and influenza may be related to the release of penicillin for widespread civilian use in 1946. For white infants the slowdown in death rates for pneumonia and influenza was not as marked, and came in 1950. Dr. Moriyama suggests that the use patterns and the effectiveness of antibiotics were not the same for the two groups.

The hard core of the infant mortality problem still remains relatively unconquered. The death rate for congenital malformations and diseases of early infancy such as birth injuries, asphyxia of the newborn infant, and premature delivery has remained fairly high for many years. Dr. Moriyama therefore concludes that no substantial progress will be made in further reducing infant mortality until there is a research break-through in dealing with these conditions of early infancy.

DEATHS

Adams, Herbert William Ⓜ Boston; University of the City of New York Medical Department, 1884; also a pharmacist and dentist; on Aug. 28, 1957, New York University gave him its presidential citation on his 100th birthday, honoring him as the university's oldest living holder of a diploma; died in Brookline, Mass., May 7, aged 102, of arteriosclerotic heart disease and pneumonia.

Amster, Julius Lewis Ⓜ New York City; born in New York City Jan. 26, 1879; Cornell University Medical College, New York City, 1902; past-president of the Bronx County Medical Society; founder and past-president of the Bronx Surgical Society: founder and past-president of the American Society of Regional Anesthesia; fellow of the New York Academy of Medicine and the American Public Health Association; served as commissioner of health for New York City; attending surgeon at the Penitentiary and Workhouse Hospital of New York City; consulting surgeon at the Manhattan State Hospital; gastrointestinal consultant to New York City Cancer Institute; consulting surgeon at the Morrisania City Hospital, where he was co-founder, and founder of the J. Lewis Amster Medical Library; consulting surgeon at the Bronx Hospital; attending surgeon at the Bronx Eye and Ear Hospital, Jewish Memorial Hospital, and Mount Eden General Hospital, where he died May 4, aged 81, of carcinoma of the stomach with metastasis to the liver.

Batchelor, Joe Exton Ⓜ Haynesville, La.; Baylor University College of Medicine, Dallas, Texas, 1933; on the staff of the Haynesville General Hospital, where he died April 21, aged 51, of cirrhosis of liver.

Beesley, Nellie Everitt, Brooklyn; Woman's Medical College of Pennsylvania, Philadelphia, 1896; died May 2, aged 85, of cerebral hemorrhage.

Beil, Arthur Randall Ⓜ Flushing, N. Y.; Cornell University Medical College, New York City, 1929; veteran of World War II; fellow of the American College of Surgeons; consultant at the Lutheran Medical Center and director in the department of obstetrics and gynecology at the Methodist Hospital in Brooklyn, where he died May 3, aged 58, of cerebral hemorrhage.

Bloom, Myer Sol, Binghamton, N. Y.; Syracuse University College of Medicine, 1915; veteran of World War I; member of the Industrial Medical Association; on the staffs of the Binghamton City Hospital and Our Lady of Lourdes Hospital; died May 4, aged 69, of myocardial infarction.

Brown, Harry Richard Ⓜ Beatrice, Neb.; St. Louis University School of Medicine, 1907; for many years member of the school board; associated with the Lutheran Hospital and the Mennonite Deaconess Home and Hospital, where he died April 27, aged 77, of carcinoma of the lung.

Cahill, John Joseph, Brooklyn; Albany (N. Y.) Medical College, 1912; member of the staff of the Samaritan Hospital; died March 27, aged 75, of bronchopneumonia.

Childs, Donald Smythe Ⓜ Syracuse, N. Y.; born in Syracuse Jan. 5, 1888; Syracuse University College of Medicine, 1909; vice-chairman, Section on Radiology, American Medical Association, 1955-1956, and chairman, 1956-1957; past-president of the American Board of Radiology, of which he was trustee from 1940; for many years secretary-treasurer of the Radiological Society of North America, Inc., which in 1949 presented him with the Gold Medal Award for outstanding contribution to the science of radiology; business manager of the scientific journal of the society, *Radiology*; past-president of Syracuse Academy of Medicine; fellow of the American College of Radiology; member of the American Roentgen Ray Society and the Central New York Roentgen Ray Society; became emeritus professor of radiology at his alma mater, where he joined the faculty in 1913; consulting radiologist at Syracuse Psychopathic Hospital and the Marcy (N. Y.) State Hospital; radiologist at St. Joseph's Hospital from 1914 to 1948, when he became senior attending radiologist; radiologist at St. Mary's Hospital; from 1924 to 1948 radiologist at the City Hospital; a member of the board of directors of the Blue Cross Plan and Blue Shield Plan of Syracuse; died in the Syracuse Memorial Hospital April 27, aged 72, of heart disease.

Clock, Ralph Oakley, Pittsfield, Mass.; University of Pennsylvania Department of Medicine, Philadelphia, 1904; fellow of the American College of Physicians; adjunct professor of medicine, emeritus, New York Polyclinic Medical School and Hospital in New York City; past-president and secretary of the Rockland County (N. Y.) Medical Society; consulting physician at the Nyack (N. Y.) Hospital; died April 30, aged 80, of coronary thrombosis.

Cooke, Robert Anderson, New York City; born Aug. 17, 1880; Columbia University College of Physicians and Surgeons, New York City, 1904;

Ⓜ Indicates Member of the American Medical Association.

specialist certified by the American Board of Internal Medicine; served on the faculty of Cornell University Medical College; member of the Association of American Physicians, American Society for Clinical Investigation, and the American Clinical and Climatological Association; fellow of the American College of Physicians; the founder and first president of the Society for the Study of Asthma and Allied Conditions, now known as the American Academy of Allergy; chairman of the scientific and educational council of the Allergy Foundation of America; director of the Institute of Allergy at the Roosevelt Hospital, where in 1955 he was honored when his portrait, commissioned by a group of physicians who had been his students, was unveiled and presented in appreciation of "his outstanding work in the field of allergy"; founded the first clinic devoted to allergy diseases at New York Hospital many years ago; in 1932 it was moved to the Roosevelt Hospital; author of a book entitled "Allergy in Theory and Practice" published in 1947; died in the Roosevelt Hospital May 7, aged 79, of arteriosclerotic heart disease.

Davis, Lewis Clifton, Gordo, Ala.; Emory University School of Medicine, Atlanta, 1915; veteran of World War I; served on the school board; a member of the Pickens County Commissioners for 20 years; on the staff of the North Pickens Hospital in Reform; died May 1, aged 67, of acute coronary occlusion.

Dawson, Stephen Augustine, St. Petersburg, Fla.; University of Pittsburgh School of Medicine, 1912; for many years on the staff of the Mound Park Hospital, where he died April 29, aged 70.

Dewey, Julius Edward, Montpelier, Vt.; University of Vermont College of Medicine, Burlington, 1904; served with the Veterans Administration; died April 23, aged 82, of arteriolar nephrosclerosis.

Dyer, Joseph Francis, Washington, D. C.; Howard University College of Medicine, Washington, 1912; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; clinical assistant professor of otolaryngology at his alma mater; on the staff of the Freedmen's Hospital; died May 7, aged 71, of heart failure.

Egbert, Ivan Raleigh Ⓜ Arco, Idaho; Rush Medical College, Chicago, 1920; died April 26, aged 69, of myocardial infarction.

Ehle, Vernon R., Johnstown, N. Y.; Albany (N. Y.) Medical College, 1906; veteran of World War I; served on the staff of the Nathan Littauer Hospital in Gloversville; died in the Johnstown Hospital April 23, aged 78, of coronary occlusion.

Eskew, Milner Hubbard Ⓜ Uniontown, Ala.; University of Virginia School of Medicine, Charlottesville, 1917; served in the regular Army; member of the American Academy of General Practice; formerly on the staff of the Vaughan Memorial Hospital in Selma; died in Selma, Ala., April 16, aged 67, of cancer of the colon.

Evans, George Phillips Ⓜ Largo, Fla.; College of Physicians and Surgeons, Baltimore, 1908; served as superintendent of the Andrew S. Rowan Memorial Home at Sweet Springs, W. Va.; served four terms as a member of the West Virginia House of Delegates; formerly associated with the Welch (W. Va.) Emergency Hospital; died April 25, aged 77, of coronary occlusion.

Farrington, Reno Kirby Ⓜ Thomasville, N. C.; University of Cincinnati College of Medicine, 1925; associated with the City Memorial Hospital, where he died April 28, aged 59, of acute myocardial infarction.

Fearn, John William, Fontana, Calif.; Maryland Medical College, Baltimore, 1911; died March 24, aged 83, of coronary occlusion.

Ferris, William Thomas, Chicago; Georgetown University School of Medicine, Washington, D. C., 1924; veteran of World War II; died April 27, aged 60, of arteriosclerotic heart disease.

Findley, Cleveland Ward, Vidalia, Ga.; Atlanta School of Medicine, 1912; veteran of World War I; died in the Veterans Administration Center, Dublin, Jan. 21, aged 73, of arteriosclerotic heart disease.

Fleming, Edward Lee, Indiana, Pa.; Chicago College of Medicine and Surgery, 1909; for many years county coroner; associated with the Indiana Hospital; died May 2, aged 75, of carcinoma.

Gilligan, John Henry Ⓜ Arlington, Va.; born in Pittston, Pa., Aug. 22, 1904; Georgetown University School of Medicine, Washington, D. C., 1929; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; clinical associate professor of otorhinolaryngology at the Georgetown University School of Medicine in Washington, D. C.; served on the staffs of the District of Columbia General Hospital, Washington Medical Center, Children's Hospital, Georgetown Hospital, and the George Washington University Hospital, all in Washington, D. C., and the Arlington Hospital; drowned in the yacht basin in Rose Haven, Md., April 29, aged 55.

Ginsburg, Gershon, Philadelphia; University of Pennsylvania School of Medicine, Philadelphia, 1917; specialist certified by the American Board of Pathology; veteran of World War I; consultant in clinical pathology at the Albert Einstein Medical Center; died in the Northern Division, Einstein Medical Center, April 26, aged 72, of pulmonary edema, arteriosclerotic heart disease, and uremia.

Glass, Oscar, East Orange, N. J.; born in 1895; Medizinische Fakultät der Universität, Vienna, Austria, 1922; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the International College of Surgeons and the American College of Surgeons; chief of the department and attending gynecologist, St. Michael's Hospital, consultant in gynecology, Beth Israel Hospital, and attending gynecologist at the Hospital for Crippled Children, all in Newark; died May 10, aged 64, of coronary thrombosis and diabetes.

Gyland, Stephen Peter Ⓢ Tampa, Fla.; University of Pennsylvania School of Medicine, Philadelphia, 1924; member of the American Academy of General Practice; affiliated with Tampa General, St. Joseph's, and Centro Asturiano hospitals; died in the Methodist Hospital, Houston, Texas, April 15, aged 67, of myocardial infarction.

Hinchman, Clarence Paul Ⓢ Geneva, Ind.; Indiana University School of Medicine, Indianapolis, 1916; president of the medical staff of Adams County Memorial Hospital, Decatur; died in the Ball Memorial Hospital in Muncie, April 22, aged 68, of hepatitis.

Hirsch, Raymond Stephen Ⓢ Viroqua, Wis.; Marquette University School of Medicine, Milwaukee, 1930; member of the American Academy of General Practice; past-president of the Vernon County Medical Society; member of the state board of medical examiners; served overseas during World War II; died in St. Mary's Hospital, Rochester, Minn., April 25, aged 55, of lymphosarcoma.

Hubbard, Frederic George, Forman, N. D.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1903; county health officer; served as county coroner and as president of the school boards of Cayuga and Cogswell; appointed selective service medical examiner for the county during World Wars I and II; died in the Britton (S. D.) General Hospital April 19, aged 83, of heart failure.

Koch, Scott Lorain Ⓢ Pittsburgh; University of Pennsylvania School of Medicine, Philadelphia, 1909; fellow of the American College of Surgeons; served on the faculty of the University of Pittsburgh School of Medicine; associated with the Eye and Ear Hospital of Pittsburgh, Presbyterian Hospital, and the Woman's Hospital; died April 17, aged 78, of cerebral hemorrhage.

Koon, Bernard Thomas, St. Louis; St. Louis University School of Medicine, 1929; member of the American Academy of General Practice and the American Psychiatric Association; veteran of World War II; served on the faculty of his alma mater; on the staffs of the Incarnate Word, Firmin Desloge, St. John's, and St. Anthony's hospitals; died May 3, aged 56, of a heart attack.

Lance, Vernal Lee, Fresno, Calif.; Emory University School of Medicine, Atlanta, 1936; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; associated with the Fresno Community, St. Agnes, and Valley Children's hospitals; died April 24, aged 50, of coronary occlusion.

Latiolais, Sydney Graves Ⓢ Dothan, Ala.; University of Tennessee College of Medicine, Memphis, 1931; member of the Radiological Society of North America, Inc., and the American Heart Association; associated with the Frasier–Ellis Hospital; died May 2, aged 53, of coronary thrombosis.

Lee, Insun, Louisville, Ky.; Severance Union Medical College, Keijo, Chosen (Seoul, Korea), 1931; interned at St. John's Riverside Hospital in Yonkers, N. Y.; served a residency at the Mountain State Hospital in Charleston, W. Va., and the Baroness Erlanger Hospital in Chattanooga, Tenn.; an anesthesiologist on the staff of the Jewish Hospital; died March 19, aged 52, of portal cirrhosis.

Leibinger, Henry Robert, Detroit; University of Illinois College of Medicine, Chicago, 1916; died in Bon Secours Hospital March 31, aged 70, of heart failure.

Leinbach, Howard Milton, Wyomissing, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1910; member of the American Academy of Orthopedic Surgery; chief of orthopedics at the Reading (Pa.) Hospital, where he died April 22, aged 75, of carcinoma of the colon.

Levy, Jacob Ⓢ Brooklyn; University of Illinois College of Medicine, Chicago, 1927; member of the American Academy of General Practice; veteran of World War II; assistant physician at Unity Hospital, where he died Feb. 9, aged 61, of myocardial infarction.

Lojacono, Salvatore, Dearborn, Mich.; Universita degli Studi di Padova. Facolta di Medicina e Chirurgia, Italy, 1917; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; died in the Wayne County General Hospital and Infirmary, Eloise, Feb. 7, aged 78, of acute peritonitis and volvulus of the colon.

McCarthy, Joseph Justin Ⓢ St. Paul; St. Louis University School of Medicine, 1928; veteran of World War I; police surgeon; died in St. Joseph's Hospital April 23, aged 65, of hemorrhage from malignant ulcer in pharynx and squamous-cell carcinoma of the pharynx.

McClanahan, James H. Ⓢ White Bear Lake, Minn.; Northwestern University Medical School, Chicago, 1909; on the staff of St. John's Hospital, St. Paul; died in Columbus, Ohio, April 14, aged 77, of carcinoma of the prostate.

McEuen, Harry Bernard Ⓜ Jacksonville, Fla.; University of Louisville (Ky.) Medical Department, 1909; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; past-president of the Florida Radiological Society; veteran of World War I; died April 15, aged 71, of bronchogenic carcinoma.

McMurray, William John Ⓜ Bronxville, N. Y.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1924; served in the Canadian Army during World War I; on the staff of the Lawrence Hospital; died in the Methodist Hospital, Brooklyn, April 1, aged 60, of arteriosclerotic heart disease.

Martin, Thomas Philip, Minneapolis; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1902; veteran of World War I; practiced in Arlington, Minn., where he was city and township health officer for many years and on the staff of the Arlington Hospital; died May 4, aged 86, of pneumonia and esophageal ulcer.

Mason, Howard Harris Ⓜ New York City; Columbia University College of Physicians and Surgeons, New York City, 1904; specialist certified by the American Board of Pediatrics; fellow of the American Pediatric Society; consultant in pediatrics at the Babies Hospital, Vanderbilt Clinic, Greenwich (Conn.) Hospital, and the New York Orthopedic Dispensary and Hospital; died May 8, aged 81, of myasthenia gravis.

Matheson, Robert Arthur, Raeford, N. C.; Jefferson Medical College of Philadelphia, 1926; member of the American Academy of General Practice; veteran of World War I; in 1940 became a major in the National Guard; died April 24, aged 62, of massive myocardial infarction.

Mathewsian, Mehron H., Louisville, Ky.; University of Louisville Medical Department, 1914; veteran of World War I; at one time chief medical officer for the Louisville and Nashville Railroad; died in the Veterans Administration Hospital, Lake City, Fla., April 11, aged 77, of suppurative pyelonephritis.

Maxson, Frank S., Milwaukee; Milwaukee Medical College, 1900; veteran of the Spanish-American War; served on the staff of Milwaukee Hospital, where he died May 1, aged 83, of metastatic carcinoma of the liver due to a gastric carcinoma.

Morton, David Holmes, Elmwood, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1904; for many years served on the grade and high school boards and was president of both boards for several years; on the courtesy staff of the Methodist Hospital in Peoria, where he died April 19, aged 79, of chronic pyelonephritis.

Moseley, Samuel Olliphant Ⓜ Selma, Ala.; Tulane University School of Medicine, New Orleans, 1920; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; associated with the Good Samaritan Hospital and the Selma Baptist Hospital, where he died April 14, aged 64, of squamous-cell carcinoma with generalized metastasis.

Murphy, Harold Oliver, Warsaw, Ind.; Indiana University School of Medicine, Indianapolis, 1952; interned at the Methodist Hospital in Indianapolis; veteran of World War II; member of the American Academy of General Practice; died April 27, aged 38, of bronchopneumonia.

Opre, Beattrice Carpenter Ⓜ Victoria, Ill.; Chicago College of Medicine and Surgery, 1908; died in the Galesburg Cottage Hospital March 27, aged 81, of coronary occlusion.

Orr, Charles Collins Ⓜ Asheville, N. C.; born Oct. 5, 1874; University of Maryland School of Medicine, Baltimore, 1904; specialist certified by the American Board of Internal Medicine; member of the American College of Chest Physicians and the American Trudeau Society; fellow of the American College of Physicians; served as president of the Buncombe County Medical Society; past-president of the Tri-State Medical Association of the Carolinas and Virginia; formerly member of the state board of health; veteran of World War I; served on the staffs of Ashton Park, Mission, and St. Joseph's hospitals; died in St. Joseph's Hospital April 2, aged 85, of coronary thrombosis.

Palmisano, Dominic Andrew Ⓜ Chicago; Chicago Medical School, 1923; served as president of the Northwest Branch of the Chicago Medical Society; veteran of World War I; on the staff of St. Elizabeth Hospital, where he died May 3, aged 60, of cavernous hemangiosarcoma of liver.

Parker, James Harold Ⓜ Oklahoma City, Okla.; University of Louisville (Ky.) Medical Department, 1910; formerly superintendent of the State Hospital number 4 in Farmington, Mo., and State Hospital number 2 in St. Joseph, Mo.; retired from the Veterans Administration Oct. 31, 1956; served on the staffs of the Veterans Administration hospitals in Waco, Texas, Sheridan, Wyo., and Muskogee and Oklahoma City; died in the Veterans Administration Hospital April 21, aged 73, of subdural hematoma (accidental fall).

Phelps, Flora May, Long Beach, Calif.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1901; served on the staffs of the Long Beach Community and Seaside Memorial hospitals; died May 3, aged 89, of congestive heart failure.

Pitts, Arthur Emerson, Albany, N. Y.; Albany Medical College, 1909; served on the faculty of his alma mater; affiliated with Albany Hospital; died April 21, aged 74.

Rettaliata, Anthony Leo, Baltimore; born in Baltimore Nov. 23, 1874; University of Maryland School of Medicine, Baltimore, 1899; his career as a staff member of the city health department began with his appointment as health warden on Jan. 1, 1911; from then served on a part-time basis in the capacity of school medical examiner and investigator in communicable diseases until his promotion in 1933 to full-time health officer assigned to the Eastern Health District; later accepted a part-time position as senior medical investigator with the health department and served in this capacity until the end of 1954, when he retired; associated with St. Joseph's and Sinai hospitals; died May 6, aged 85, of coronary disease.

Richardson, Cleves Ⓢ Louisville, Ky.; Jefferson Medical College of Philadelphia, 1913; veteran of World War I; associated with St. Joseph Infirmary and the Jewish Hospital, where he died April 20, aged 69, of congestive heart failure.

Riley, James O. Ⓢ Quincy, Miss.; Vanderbilt University School of Medicine, Nashville, Tenn., 1894; died in the Gilmore Sanitarium in Amory April 15, aged 91, of cerebral thrombosis.

Rood, Morris Ⓢ Northridge, Calif.; Georgetown University School of Medicine, Washington, D. C., 1931; interned at the Coney Island Hospital in Brooklyn; member of the American Academy of General Practice; veteran of World War II; associated with the Northridge Hospital; past-president of the Northridge Chamber of Commerce; died April 22, aged 52, of subarachnoid hemorrhage.

Rooney, Edward Joseph, Toledo, Ohio; Loyola University School of Medicine, Chicago, 1921; on the staffs of the Flower Hospital, St. Charles Hospital, and the Mercy Hospital, where he died April 21, aged 67, of cancer.

Rose, Abraham Hewitt Ⓢ Smithfield, N. C.; Jefferson Medical College of Philadelphia, 1906; served on the board of education; for many years county physician; on the staff of the Johnston Memorial Hospital, where he died April 21, aged 79, of congestive heart failure.

Seale, Joseph Kendrick Jr., Greenville, Miss.; University of Tennessee College of Medicine, Memphis, 1949; interned at St. Louis City Hospital; served a residency at the University Hospitals in Cleveland; since July, 1959, clinical instructor in the department of anesthesiology at the University of Mississippi School of Medicine in Jackson, where he joined the faculty as assistant professor of surgery (anesthesiology) on July 1, 1957; served as senior member of the department until June 30, 1959; anesthesiologist for the General and King's Daughters hospitals; drowned May 2, aged 33, in a boating accident in the Mississippi River.

Seidel, Karl Edward Ⓢ Grand Rapids, Mich.; University of Michigan Medical School, Ann Arbor, 1939; veteran of World War II; on the staff of the Butterworth Hospital, where he died May 3, aged 47, of coronary disease.

Sicomo, Joseph Flavianus, New Orleans; Tulane University School of Medicine, New Orleans, 1923; served on the faculty of his alma mater; associated with the Montelepre Memorial Hospital, where he died April 22, aged 63, of aneurysm.

Simmons, Howard Jackson, South Sioux City, Neb.; Jefferson Medical College of Philadelphia, 1911; veteran of World War I; died in Sioux City, Iowa, April 23, aged 74, of cerebral thrombosis.

Stein, Ignatius Louis Ⓢ Flushing, N. Y.; University and Bellevue Hospital Medical College, New York City, 1915; fellow of the American College of Surgeons; veteran of World Wars I and II; associated with St. John's Long Island City Hospital in Long Island City; died April 18, aged 66.

Stewart, James Kennedy Ⓢ Wheeling, W. Va.; Jefferson Medical College of Philadelphia, 1929; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; veteran of World War II; associated with the Ohio Valley General Hospital and the Wheeling Hospital; died April 28, aged 59, of arteriosclerotic heart disease.

Sutter, Loe Albright, Wichita, Kan.; University of Colorado School of Medicine, Denver, 1912; affiliated with the Wesley Hospital, where he died April 26, aged 77, of coronary occlusion.

Tooker, Mary Elliot Fitch, Summit, N. J.; Woman's Medical College of Pennsylvania, Philadelphia, 1900; a medical missionary in China for 37 years; died April 28, aged 85, of pneumonia.

Warriner, William Lucian Ⓢ Topeka, Kan.; Chicago Medical College, 1888; served as professor of physiology at the Kansas Medical College; died April 23, aged 97, of arteriosclerotic heart disease.

Wojtalewicz, Lucian Francis, Chicago; Northwestern University Medical School, Chicago, 1926; veteran of World War II; died April 2, aged 61, of acute coronary occlusion.

Woolsey, Chester Howard Ⓢ Woodside, Calif.; Medical Department of the University of California, San Francisco, 1901; served as city bacteriologist in San Francisco, where he was a member of the board of health; veteran of World War I; died April 21, aged 89, of subarachnoid hemorrhage.

FOREIGN LETTERS

FRANCE

Prevention of Embolisms in Auricular Fibrillation.—At the meeting of the Medical Society of the Hospitals of Paris, P. Maurice and co-workers, using a series of 103 patients with cardiac diseases, reported on the prevention of embolisms of the pulmonary arteries which occurred in patients with cardiac diseases that were associated with auricular fibrillation or flutter. There were 94 patients with valvular rheumatic heart disease, 6 with idiopathic auricular fibrillation, and 3 with arterial hypertension. Of the 103 patients 49 had cardiac insufficiency. The treatment consisted in the administration of either phenindione in an average dose of 65 mg. daily, or ethyl biscoumacetate in an average dose of 300 mg. daily for periods averaging about 18 months. The prothrombin time was lowered to 30%. Epistaxis occurred in six patients and hematuria occurred in one. Interruption of treatment for three days was sufficient to stop these hemorrhages.

In the two years before treatment the patients averaged one embolism in 16 months of observation. On the other hand, during the treatment with anticoagulants, which included the 10 days after the eventual withdrawal of treatment, the patients averaged one embolism in 137 months of observation. The emboli in about one-half of the patients who developed them, occurred 5 to 10 days after the anticoagulant treatment was withdrawn. In one third, embolism was caused by insufficient or ineffective treatment. The authors concluded that continuous examination of the constituents of the blood is indispensable and should be done every fifth day in the beginning, then every two to four months in order to maintain the prothrombin level around 30%. On the other hand, one should exclude from this treatment all those patients who have ulcers of the digestive tract, severe hepatic or renal insufficiency, or hemorrhagic diseases.

Electrophoresis for Cancer.—J. Janet and co-workers (*Therapy*, no. 6, 1959) gave N-desacethylthiocolchicine (R 261) by electrophoresis to patients with cancer. Considering the fact that iontophoresis is ineffective because of skin resistance, various instruments have been devised for ionization of the mucosa, particularly that of the digestive tract. For regulation of cellular respiration this treatment by R 261 was combined with giving such drugs as ascorbic acid, vitamin B complex, trace elements, and perfusions with cytochrome B. Electrophoresis with R 261 provoked transitory edema at the site of the tumor, but after a few 15-minute sessions daily or every second day, a gradual diminution of the neoplastic tissues and even breaking down of significant fragments took place.

Disintegration of the tumor may cause hemorrhages, and, on the other hand, the presence of the products of cell destruction in the blood may cause shock. Leukopenia did not occur because only a small quantity of the drug was introduced into the circulation. The authors used the treatment on those patients who were critically ill although R 261 arrested the growth of the tumor and alleviated pain, it could not prevent the decline of the patient's general condition.

INDIA

Myelofibrosis.—M. K. Sandozi (*J. Assoc. Physicians India* 8:155, [March] 1960) reported four cases of myelofibrosis in patients with marked enlargement of the spleen, anemia, fibrosis of marrow elements, and evidence of extramedullary hemopoiesis. One of the patients was an 18-year-old boy who, when first seen, had been ill not more than three months. This is probably the youngest patient with myelofibrosis to be reported. The disease is usually observed in middle-aged or older patients with a history of prolonged illness. The other patients in this series were 36, 45, and 60 years of age, respectively.

In the case of the 60-year-old patient, leukocyte counts and nucleated red cell counts per 100 leukocytes in the peripheral blood before and after an injection of epinephrine were made. The leukocyte count rose to two or three times its normal value, and the differential count showed a similar rise in nucleated red cells. Such a change is not noted in patients with splenomegaly which might be due to any other cause. Another characteristic feature was the marked cachexia due to hypoproteinemia which suggested the possible role of low serum protein levels in suppressing the erythropoietic activity of the marrow. The striking association of hypoproteinemia and cachexia in this series was more significant than could be expected on the basis of the frequency of malnutrition in the population. These patients did not show such signs of malnutrition as nutritional edema or liver insufficiency but they had a marked weight loss and a cachectic appearance.

These findings suggested a close relationship between myelofibrosis and protein malnutrition and put the disease in the group of nutritional disorders. It is important to differentiate this disease from chronic myeloid leukemia because deep irradiation of the spleen in patients with myelofibrosis aggravates the disease, and splenectomy is to be avoided as these patients need their spleens for hemopoiesis.

The items in these letters are contributed by regular correspondents in the various foreign countries.

ACTH and cortisone were also tried but they caused worsening of the condition. The authors believe that identification of this syndrome is important in tropical countries (many patients with hypoproteinemia and anemia are seen in India), and its management depends on a correct diagnosis.

Tropical Eosinophilia.—Bhargava H. S. and co-workers (*J. Assoc. Physicians India* 8:117 [March] 1960) compared the effectiveness of orally and parenterally administered diethylcarbamazine in the treatment of tropical eosinophilia. Although no significant difference was noted in the results of treatment with the two routes of administration, parenteral therapy required an average total dose of 800 mg. and oral therapy required 4.2 Gm. Relapses and exacerbations were, however, more common with parenteral therapy, which also induced toxic side-effects in some patients.

Examination of Sputum.—After studying a large number of sputum specimens by direct smear and culture methods, Chowdhury and Ghosh (*J. Indian M. A.* 34:265 [April 1] 1960) concluded that cultural examination is by no means superior to careful and repeated smear examination for the detection of acid-fast bacilli. In a series of 783 specimens, 46.6% gave positive results on smear examination and 28.9% on cultural examination. The high incidence of positive results on smear examination was obtained in spite of the fact that most of the patients were already receiving chemotherapy. Repeated cultures yielded tubercle bacilli in only 3.4% of those whose smears showed negative results. In 50.1% of the patients, both the methods showed negative results. Sensitivity tests were made using the different antituberculosis drugs in patients whose sputum or laryngeal swab culture or both gave positive results. Of the three antituberculosis drugs, streptomycin, isoniazid, and PAS, streptomycin proved to be the most sensitive. For sensitivity tests the cultural method of either the sputum or the laryngeal swab is necessary.

ISRAEL

Nutrition of Jews From Cochin.—K. Guggenheim and F. Dreyfuss (*Harefuah* 17:304, 1959) reported that the Jewish population of Israel, now over 2 million, has come from over 70 countries. The new immigrants, differing in their social and cultural patterns, are in the process of merging with those who were living in the country before 1948, the year of the establishment of the State of Israel. The old settlers, although numerically a minority, are expected to absorb the new immigrants both economically and culturally.

Many new foods and food habits have been introduced. Some oriental foods have been readily accepted, and their use is now widespread among all ethnic groups. Many food habits, however, are preserved in specific ethnic communities and have not yet become popular with the general population. Since food habits often represent the emotional ties which link the new immigrant with his country of origin, they tend to be preserved as much as possible in the new environment. Economic factors, as well as the nonavailability of certain foodstuffs, often frustrate this tendency especially in smaller ethnic groups. The problem of how new immigrants manage to obtain a satisfactory diet where the choice of food is limited and the consumer is compelled to use food to which he is not accustomed was studied by the authors in one of the smallest ethnic groups of immigrants, Jews from Cochin, South India.

A dietary survey was conducted of 82 Jewish families from Cochin. A marked change of food habits has occurred since these people immigrated to Israel. Most conspicuous is the acceptance of wheat products which replace rice to a large extent as a staple food. In spite of changing food habits, the general level of consumption of nutrients was satisfactory, although the intake of calcium, vitamin A, and ascorbic acid was inadequate in 13 to 22% of households. The mean dietary rating of all households, however, was good. Enrichment of flour with soya meal, calcium, riboflavin, and of margarine with vitamins A and D was an important protective measure.

Serum Lipids.—D. Brunner and co-workers (*Israel M. J.* 17:177, 1958) stated that Jews of European extraction (Ashkenazis) have incidence of coronary heart disease as high as that of most European and American groups. Yemenite Jews, however, rarely suffer from myocardial infarction. Although the serum cholesterol and phospholipid levels of middle-aged Ashkenazi Jews are similar to those reported from Europe and America, those of middle-aged Yemenite Jews are much lower. The authors studied 41 Yemenite men who were 18 to 20 years of age and 35 who were 30 to 50. Mostly these were of the lower economic class and engaged in manual labor. They also studied 45 Ashkenazis aged 18 to 20 years who were, for the most part, students from the upper middle economic class of families long settled in Israel, and an older group of 115 Ashkenazis, aged 30 to 52, that included both manual and sedentary workers without signs of coronary heart disease. A third group of 36 Ashkenazis, aged 30 to 55, consisted of members of a farm settlement who performed hard physical labor. The authors concluded that the apparent tendency of the serum cholesterol level to rise with age is not a physiological concomitant of the aging process but may be the result of environmental factors.

Health Service for the Bedouin.—The Negev Bedouin inhabit an area of 1,100 sq. km. which is about 5% of the total area of Israel. The greatest achievements in Israel's efforts to convince the Bedouin of the benefits of civilization have been in the sphere of health services. In 1949, when these services were initiated, the organizers met with district and suspicion among the Bedouin, who practiced witchcraft and believed in the teachings of the dervishes. Today the five clinics established in the Bedouin centers are constantly busy. Jewish doctors visit the Bedouin tribes and examine those who are still unwilling to visit a clinic. The incidence of tuberculosis among the Bedouin is five times as great as among the Jewish population, but since most tuberculous patients are now hospitalized immediately, there has been a marked fall in the death rate.

SWEDEN

Radioactive Iodine For Mitral Valvular Disease.—Eliasch and co-workers (*Acta chir. scandinav.* [supp.] 245:223-236, 1959) gave radioactive iodine to 24 euthyroid patients with mitral valvular disease. Follow-up studies were made after at least five years. Hypothyroidism was produced in most of the patients. Associated symptoms were partially relieved by giving thyroid and chlorothiazide. Most of the 15 patients who lived longer than five years were improved. The hemodynamic response to treatment was studied in nine patients. In four of these, pulmonary arterial hypertension was alleviated which was not necessarily associated with reduction in the cardiac output. The authors suggested that ablation of the thyroid gland by radioiodine could be a valuable therapeutic measure for relief of mitral valvular disease in those patients for whom operation was not advised.

Meckel's Diverticulum.—Sigrid Söderlund (*Acta chir. scandinav.* [supp.] 248:233, 1959) surveyed a series of 413 patients with Meckel's diverticulum (337 children less than 16 years old and 76 patients aged 16 and over). In 271 (222 children and 49 adults) Meckel's diverticulum was an incidental finding. The salient clinical feature was rectal hemorrhage which was present in 75% of the patients. The author suggested that greater attention than hitherto shown should be focused on the possibility of peptic ulcer in a Meckel's diverticulum in adults as a cause of rectal hemorrhage. The treatment was surgical. The prognosis was usually good (only one death occurred in those with such ulcers in the present series). Intestinal obstruction was present in 59 patients, and of these, 9 died. Intussusception was found in 19 patients, all children. In these cases the author recommended that primary exteriorization of the intestinal segment involved or of the Meckel's diverticulum should be performed to a greater extent than before. Diverticulitis was present in 24 patients. Perforation occurred in 12 patients, 2 of whom died. Treatment generally consisted of diverticulectomy. Resection of the small intestine was occasionally necessary. The author concluded that, whenever possible, a search should be made for Meckel's diverticulum when a laparotomy is performed for other reasons and that it should be removed when it is detected incidentally.

Complications of Epidural and Spinal Anesthesia.—L. E. Almgård (*Acta chir. scandinav.* 117:433-445, 1959) stated that only 33% of the hospitals in Sweden had anesthesiologists and that consequently spinal anesthesia was used in a fairly high proportion of cases. The author reported a series of 5,404 patients of whom 3,500 were given epidural and 1,904 spinal anesthesia. In the early part of the investigation, spinal anesthesia predominated. It was possible to follow-up 3,603 patients, or 72%. Falls in blood pressure exceeding 50 mm. Hg and high blocks with respiratory paralysis were as frequently associated with epidural as with spinal anesthesia. Postoperative headache and other neurological complications (with the exception of abducent nerve paresis) were rare in the group given epidural anesthesia. Paresis of the abducent nerve complicated the two forms of anesthesia about equally. The death rate was roughly the same in the two groups.

Epidural anesthesia was less effective and more frequently required supplementary anesthesia. Lidocaine in 1% solution with epinephrine was the agent recommended for all patients undergoing epidural anesthesia. A 2% solution of lidocaine with epinephrine should be used only in younger patients. The author believed that epidural anesthesia should be used more frequently than spinal anesthesia in abdominal, gynecologic, and lower extremity surgery whether or not anesthesiologists were employed. The incidence of complications at operation was about equal in the groups given epidural and spinal anesthesia. The author concluded that as postspinal complications were rare when epidural anesthesia was used, this form was less troublesome to the patient than spinal anesthesia would be.

UNITED KINGDOM

Institute of Comparative Medicine.—The Nuffield Foundation has made a grant of $280,000 to the Zoological Society of London for the founding of an institute of comparative medicine and for the provision of two senior research fellowships. The council of the society has requested that Lord Nuffield's name be associated with the title of the new institute, which will offer an opportunity for increased knowledge of disease in animals, now being studied in the society's present animal hospital.

A committee of medical and veterinary specialists under the chairmanship of Sir Roy Cameron, professor of pathology at University College Hospital, London, and a planning group under Prof. G. Payling Wright, Guy's Hospital, London, has been appointed to help with the organization of the new institute.

Inadequate Telephone Coverage.—It is essential that a doctor maintain telephone coverage for 24 hours a day. Neglect of the latter resulted in a plastic surgeon being sued by a patient whom he had advised to undergo a plastic repair operation for excess fat under the eyelids. He agreed to do the operation while the patient was placed under a local anesthetic in the hospital outpatient department. The court held that, although failure to insist on inpatient care did not constitute professional negligence, it did increase the risk of a postoperative mishap. The patient sued the surgeon, not for negligence during the operation, but for the aftercare. Bleeding occurred within 48 hours after the operation and resulted in permanent disfigurement. The court held that the surgeon, or his qualified deputy, should have been available to deal with the emergency. In the opinion of the court, failure to meet this requirement amounted to professional negligence, and damages of $4,200 were awarded to the patient.

Leucine and Pellagra.—Although pellagra has long been known to be predominantly a disease of corn eaters, Gopalan and Srikantia (*Lancet* 1:954, 1960) found that pellagra also occurs in India in areas where millet is eaten. They have compared the composition of these two cereals and find that they both have a high leucine content. The average daily intake of protein of the pellagrins investigated in an area where large quantities of millet were eaten was 45 Gm. The authors investigated the effect of leucine on the urinary excretion of N-methylnicotinamide (NMN) in healthy volunteers and pellagrins. In both groups leucine increased the urinary excretion of NMN; it increased by 50% over the basal level after 5 Gm. of L-leucine was given. There were no changes in the blood nicotinic acid. Isocaloric replacement of rice in the diet by millet also brought about an increase in the urinary excretion of NMN in healthy subjects and pellagrins. Oral administration of 20 to 30 Gm. of L-leucine daily to two pellagrins caused a temporary deterioration of their mental condition; this was reversed when the administration of leucine was discontinued and nicotinic acid was given.

The authors suggested that the greater prevalence of pellagra in millet eaters than in rice eaters is not due to deficiency in tryptophan or poor availability of its nicotinic acid but to the high leucine content of millet. In some way this amino acid appeared to deplete the tissues of their nicotinic acid. It was calculated that 5 Gm. of L-leucine daily could divert 3.5 mg. of nicotinic acid daily from the metabolic pool, and if the diet is already marginal in its nicotinic acid content, such a diversion could lower the stores of nicotinic acid sufficiently to precipitate pellagra.

Paromomycin.—Several antibacterial drugs can control or shorten an attack of shigella dysentery, but complete eradication of the organism from the intestine is more difficult, and persistent excretion of the infecting organism for six weeks or longer is relatively common. Coles and co-workers (*Lancet* 1:944, 1960) used paromomycin for the treatment and eradication of shigella and salmonella infections. This antibiotic, which is derived from a strain of streptomyces, is effective against gram-negative organisms. It was given by mouth in a syrup containing 1 Gm. in 4 ml. or in 150-mg. capsules. The daily dose was 80 mg. per kilogram of body weight.

Paromomycin was effective in eradicating Shigella sonnei in a large proportion of patients and persons who were carriers. In this respect it compared well with other forms of treatment, as clearance occurred in 25 of 27 patients in 8 to 24 days and was as effective in persons who were chronic carriers as in patients who had acute cases. The average period with other drugs was 27 days. Paromomycin was less effective in the treatment of salmonella infections. No serious toxic reactions or superinfections developed. The action of paromomycin was mainly bacteriostatic against Sh. sonnei and Salmonella typhi. Although no drug has yet been found that consistently eliminates these species from persistent excreters, the results obtained with paromomycin seemed promising.

Tropical Eosinophilia.—Evidence is accumulating that filarial infection is the cause of tropical eosinophilia. In this condition there is a consistently high titer of filarial complement-fixing antibodies in the serum and a clinical, hematological, and serologic response to therapy with the antifilarial drug, diethylcarbamazine. The blood shows no microfilarias, although these have been found in the lymph nodes. Webb and co-workers (*Lancet* 1:835, 1960) reported the finding of microfilarias in the lungs, liver, and lymph nodes of 10 patients who had tropical eosinophilia. The microfilarias recovered were identified as Wucheria bancrofti. The authors believed that tropical eosinophilia in all its possible clinical manifestations was usually due to some form of filaria. During the active phase of the disease, microfilarias continue to be liberated from the adult worm only to become trapped in the tissues where they die and excite the characteristic eosinophilia. After the microfilarias have been released into the blood stream, they are trapped in the first set of capillaries that they enter, usually in the lungs, which would account for the predominance of pulmonary involvement in tropical eosinophilia.

CORRESPONDENCE

BRITISH COMMONS

To the Editor:—I did not understand the use of the term "Commons" in your editorial that referred to Vaughan's book in THE JOURNAL, June 11, page 682.

J. A. T.
New York

It was not clear to me either so I wrote to Dr. Hugh Clegg, editor of the *British Medical Journal*, who replied as follows.

"In reply to your letter about Paul Vaughan's book, I had best give you the definition of 'Doctors' Commons' from the big Oxford: 'The common table and dining-hall of the Association or College of Doctors of Civil Law in London; hence, the buildings occupied and used by these as an incorporated Society and now the name of the site of these, to the south of St. Paul's Cathedral.'

"It has also come to mean the common dining-hall of such distinguished people. Paul Vaughan has, so to speak, made a bit of a play on the word, or rather the phrase, by transferring to the British Medical Association, a term which has hitherto been applied to lawyers."—ED.

SOCIAL PROBLEMS

To the Editor:—The present mode of social thinking—individually, in government, and in worldwide relations—may be perpetrating, in the social sphere, the sin which is cardinal in medicine: treating the symptoms of disease and overlooking the basic disease process itself. Society attempts to keep the older person when he no longer will keep himself instead of getting at the root of the disease and teaching and encouraging him to care for himself.

The result is the creation of law after law and tax after tax, one often negating the good created by the other. People succumb to the belief that happiness depends upon certain material benefits and neglect the spiritual and emotional side of man. They think that, if they provide the older person with a small monthly check and marginal medical care, they have thereupon done their social duty, stilled their social conscience, and done what they are able to satisfy his requirements for happiness. In so doing, they completely ignore what their own experience and that of history teaches them: that human beings are never made really happy by the simple filling of basic material needs. They neglect the spirit of the older person—his personal pride in accomplishment and the satisfaction of doing his own work, of having his own share in life, and of being independent. Instead, society hands him marginal basic material needs and thereby deadens his desires to help himself.

A more rational approach, which would fulfill his basic material needs without neglecting his spiritual needs, would be to provide the means whereby the older person would be able to help himself and thereby realize basic material and spiritual needs. Society could get closer to the treatment of the disease itself if it provided a program to fulfill this objective. Such a program might include teaching programs to enable the older person to learn new skills in accord with his physical abilities and to maintain his independence; tax legislation aimed at providing tax-sheltering to industries which hire older persons, which would encourage the growth of industries in which they could be usefully employed; and inexpensive health insurance, housing, and other material needs, so that an older person would find these accessible to his means but would still be encouraged to provide them for himself.

Instead, society follows the ridiculous philosophy that it must provide the older person not only with basic material needs without any effort on his part but also with recreational facilities to make use of the idle time which it has created for him. This philosophy is based on the naive idea that he is being made happy by such provisions. The average man knows that happiness is not achieved this way but comes as a byproduct of creative effort and the satisfaction one feels in carrying his honest share of the load and maintaining his own independence.

This philosophy of taking care of the needs of others has been so much implanted in society by the "creeping socialism" of the past three decades that the people themselves are rapidly losing their sense of individual freedom. This idea has been ingrained so deeply into the soul of society that people no longer seek to care for themselves; they have come to accept the idea that others should care for them. They have listened so often to the speeches of political votegetters who promise them a great many things that they believe they can get anything free. They have been so effectively infused with propaganda that they forget that there is nothing in this life that is free—that somewhere someone is paying for these things. They have even begun to expect something for nothing.

What a far cry this is from the spirit of the Americans of the recent past and from all that rational common sense tells people! Each election year and political crisis drives this fallacy deeper into the thinking and lives of citizens of the United States. One wonders whether the next administration, whatever it may be, will have the courage to stop treating the symptoms and begin to treat the disease.

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BOOK REVIEWS

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The Photography of Patients Including Discussions of Basic Photographic and Optical Principles and Infrared Techniques. By H. Lou Gibson, F.B.P.A., F.P.S.A. Publication number 372, American Lecture Series, monograph in Bannerstone Division of American Lectures in Medical Photography. Edited by Ralph P. Creer, Director, Department of Medical Motion Pictures and Television, Division of Communications, American Medical Association, Chicago. Second edition. Cloth. $10.50. Pp. 200, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

The first edition of this book proved to be a valuable reference work for the physician who desired photographic recording in his office, in the clinic, or during a research project. It served as a guide and a reference to the clinical photographer as well. It is an excellent introduction to the solution of photographic problems most likely to be encountered by the busy physician. During the eight years since the book was published, many new photographic techniques have come into being. New equipment and cameras have been introduced, thereby simplifying the photography of patients and lessening the chance of error. It was reasonable, therefore, to expect a new and completely rewritten second edition.

With the increasing awareness by the physician of the importance of photographing the patient, this new edition should prove to be of even more help than the first. The book is divided into 10 basic chapters, and each is prefaced by an index. The first two chapters briefly cover the fundamental purposes of a patient photography program and the importance of planning the picture. Available photographic equipment and space requirements for office and clinic are discussed.

The next two chapters describe simplified photographic techniques with the use of previously described equipment and the principles of lens properties. Both have well-organized tables of technical data regarding exposure and lighting. Lens selection is clearly explained in diagrams and text. Positioning and handling of patients who are to be photographed and planned lighting for specific effects is presented in the next two chapters. The physician, as the author implies in the book's preface, will not have to be told how to handle patients, but the photographer new to the field will welcome suggestions. The photographer should be thoroughly familiar with the lighting plans, but the physician new to the field of photography will find such plans most helpful.

Chapters seven, eight, and nine are devoted to fundamental explanations of films, filters, color processes, printing methods, and quality of print. Many poor illustrations submitted with manuscripts would convey more information if the physician-photographer had used the simple working methods presented here. The book is ended with a chapter on infrared techniques. Because of the numerous specialized applications of this medium the author does little more than introduce the subject and its possibilities. There is, however, a list of references at the end of the chapter.

The text is organized and well illustrated with black and white and color photographs. There is a curious lack of references to subject amplification literature, with the exception of infrared photography; however, this does not impair the value of this reference book. It is recommended to the physician interested in photography, the average biological photographer, and to medical libraries.

James H. Rothenberger

Research and the Ulcer Problem. By I. S. Blumenthal. Rand Corporation study. Report R-336-RC. Paper. Pp. 81, with illustrations. Rand Corporation, 1700 Main St., Santa Monica, Calif., 1960.

This paperbacked monograph contains a readable account of the present status of peptic ulcer and chronic ulcerative colitis in the United States. It is written for the intelligent layman and the physician. The discussion of the scientific aspects of these diseases and their etiology and pathogenesis is necessarily brief and incomplete; the statistical data indicates that their enormous economic importance will probably prove startling to workers in the field. A conservative estimate is made that the total economic loss due to these ulcerative disorders is over one-half billion dollars per year. In sharp contrast to this figure, the author estimates that in 1955 a total of 5 million dollars was spent in the United States in the investigation of all diseases of the digestive system combined. It is pointed out that there has been no fund-raising, disease-oriented, organization exclusively devoted to the problems of patients with peptic ulcer and chronic ulcerative colitis. Almost 10,000 people die from peptic ulcer each year in the United States, and an almost equal number die from gastritis, duodenitis, enteritis, and colitis.

The author concludes, "as causes of death the ulcerative diseases rank far below cardiovascular diseases and cancer, are roughly comparable to tuberculosis and diabetes, but considerably exceed diphtheria, polio, and multiple sclerosis." An expanded program of research in peptic ulcer and chronic ulcerative colitis is both important and urgent. The amount of money being spent annually for research is less than 1% of the estimated aggregate annual economic loss in the nation because of these diseases. Furthermore, they remain highly obscure as to origin in spite of the many attempts to ferret out the causative factors. While I would differ with this last statement, being persuaded that we actually know a great deal about the pathogenesis of peptic ulcer, nevertheless, I agree with the general thesis of the great importance of these problems and the urgent necessity for expansion of the current research activity.

Lester R. Dragstedt, M.D., Ph.D.

The Health of People Who Work. Edited by Albert Q. Maisel. Based upon reports to 1959 National Health Forum of more than 200 industrial medical directors, physicians, nurses, and management officials, public health officers, voluntary health agency officials, and other experts in various areas of occupational health. Cloth. $4.50. Pp. 268. National Health Council, 1790 Broadway, New York 19, 1960.

This book contains much valuable material and is well indexed, but it consists almost wholly of direct quotations whose lengths do not always correspond with the authority generally accorded their authors. This fact, plus the paucity of references to authoritative statements, could confuse rather than help the reader who seeks guidance in the fundamentals of occupational health.

Unfortunately, the reader who has limited acquaintance with the subject of occupational health is likely to get the impression that this is the same as the "health of people who work." Neither the book nor its references make it sufficiently clear that occupational health is essentially a program of preventive medicine in industry, whereas the "health of people who work" includes also medical care for nonoccupational illnesses and injuries. The failure of this author to consider the health of farm and hospital workers, two large categories of people who work, is unfortunate. Some of the organizations listed in Appendix A as "sources of help on occupational health" offer little, if any, such help.

B. Dixon Holland, M.D.

Principles of Orthopaedic Surgery. By Paul C. Colonna, M.D. [First edition entitled Regional Orthopaedic Surgery. Second edition.] Cloth. $22. Pp. 799, with 500 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W. 1, England, 1960.

This is a reference book for residents, orthopedists, and others with enough experience and training to be able to profit by reading and following the recommendations of a master surgeon of the bones and joints. The author has contributed many new ideas and principles which have increased knowledge of the causes of crippling conditions and the methods by which they can best be treated.

Appropriately, this book begins with a chapter in which the importance of knowledge of the physiology of the bones and joints is emphasized. In the second chapter the pathology of the bones and joints is discussed. The subject material with regard to orthopedics is divided according to regions of the body, beginning with the spine and ribs and ending with a chapter on the foot. In addition, there are chapters on neuromuscular disabilities, tumors of the bone, and the principles of braces and other apparatus. The illustrations have been selected carefully and are reproduced exceptionally well. The text is well written and easy to read. The author emphasizes the importance of knowing how to take care of all types of injuries, and the techniques he describes and recommends are those which he has found most useful in his own practice. Orthopedists and others who deal with the diseases of the spine and extremities, including injuries, should have this book readily available.

Edward L. Compere, M.D.

Principles of Cleft Palate Prosthesis: Aspects in the Rehabilitation of the Cleft Palate Individual. By Cloyd S. Harkins, D.D.S., F.A.C.D., F.I.C.D. With collaboration of William R. Harkins, D.D.S., F.A.C.D., F.I.C.D., and John F. Harkins, D.D.S., F.A.C.D., F.I.C.D. Cloth. $12. Pp. 219, with illustrations. Published for Temple University Publications by Columbia University Press, 2960 Broadway, New York 27; Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, England, 1960.

The authors have presented the prosthetic aspects in the rehabilitation of the patient with cleft palate. The book provides inclusive material on prosthetic procedures for dentists who are primarily interested in constructing a prosthesis for such a patient, but the authors ignored the new advances in orthodontia and surgery. It is pointed out that the prosthodontist is called upon not only to salvage surgical failures but to better the condition of the patient who has an acquired cleft palate due to trauma, infection, or tumor as well.

The book is profusely illustrated. Step by step it covers techniques for determining a recommendation for treatment, making a primary impression, and constructing of a study model, constructing and applying a prosthesis for the patient with a complete or incomplete cleft not surgically treated and postoperative problems. The authors then describe the prosthetic procedure in patients with cleft palates who are postoperative and edentulous. These include special procedures for young children with this condition; they give special attention to the construction of the expansive prosthesis for infants with cleft lip and cleft palate. One wonders about the possibility of injury to dental follicles incurred by this procedure. Several chapters are then devoted to the rehabilitation of the patient with emphasis on speech therapy for patients with prosthetic restorations.

The appendixes contain a series of case history and examination forms, instructions for preparation of demonstration models, patient's care of appliance, and speech evaluation. This book should be a welcome addition to the libraries of all who are interested in this problem.

Orion H. Stuteville, D.D.S., M.D.

QUESTIONS AND ANSWERS

VERUMONTANITIS

To the Editor:—*Please outline the etiology, symptoms, and treatment of verumontanitis (colliculitis or inflammation of the prostatic orifice of the prostatic portion of the urethra.)*

M.D., Wisconsin.

Answer.—Infection and inflammation limited to the verumontanum probably does not exist independently and is generally thought to be secondary to prostatitis, seminal vesiculitis, or generalized posterior urethritis. Verumontanitis may accompany acute gonorrhea, bacterial prostatitis, or nonspecific urethritis or seminal vesiculitis. Engorgement and edema of the verumontanum may occur without bacterial infection and usually results from congestion accompanying sexual excess, coitus interruptus, or sexual stimulation without ejaculation.

The symptoms are usually those of the accompanying prostatic or vesicular infection. Specific symptoms attributed to verumontanitis are said to be painful or premature ejaculation, impotence, and urinary obstruction from the swollen verumontanum. Swelling sufficient to occlude the ejaculatory ducts and interfere with sexual sensation has been ascribed to verumontanitis in the past, but it is doubtful that all the symptoms were due to inflammation of this structure alone; many functional aspects must be considered in dealing with problems of impotence.

Diagnosis is made only by direct observation of the verumontanum through the endoscope. A urethrogram may indicate actual enlargement of the verumontanum.

Treatment is directed toward elimination of infection by antibiotic or drug therapy, as indicated by direct smear and cultures of the urine and prostatic fluid. Acute infections are best treated by rest and avoidance of instrumentation of any sort. Later treatment may require prostatic massage, urethral dilation, and, perhaps, instillation of bactericidal solutions into the posterior urethra. Therapeutic procedures previously used in the treatment of this disorder, such as direct cautery of the verumontanum; application of caustic solutions, such as silver nitrate, to the verumontanum through an open endoscope; dilation of the ejaculatory ducts; and others that are often traumatic, are now generally condemned. Many of the sexual complaints treated with such measures and thought to be caused by verumontanitis probably were functional, and the results of treatment probably were due to suggestion rather than any physical changes produced. Many of the instrumental procedures previously used may cause considerable damage, discomfort, and reinfection of the posterior prostatic urethra. Such procedures are being used less frequently at present. Similarly, the diagnosis of verumontanitis is being made less often, usually only as a feature of other infections.

LIGHTS FOR SCHOOL ROOMS

To the Editor:—*A school principal and the architect differ in their opinions concerning a light fixture to be used in an elementary school. Some schools use fluorescent lights with an egg-crate type of shield beneath. Would an unprotected light be safe to use in school rooms?*

Jack Webb, M.D., Blytheville, Ark.

Answer.—The three principal factors to be considered in illumination are (1) the amount of general illumination in a room and the amount which is actually falling on the working surface, (2) avoidance of glare, and (3) the factor of contrast by which detail is clearly seen.

Although the eye can function in illumination which varies from 1 to 10,000 f.-c. (foot-candles), it has been established that the minimum requirement for reading is about 10 f.-c. for general illumination, with addition of about 15 f.-c. at the working level. Illumination measured at desk height should be about 25 f.-c.

The most efficient way to arrange this is with adequate room lighting plus a lamp on the desk. Since this is not practicable for school rooms, illumination at desk height must be maintained by overhead lighting.

Glare is difficult to define, but it is thought of as light which interferes with clear definition and tends to cause discomfort. In classrooms it is usually due to reflection of the light from glazed paper or to unshaded light sources which shine directly into the eyes. This problem can be avoided by some form of shade which will prevent direct radiation to the eyes.

I do not believe contrast to be a particular problem, because generally school work is concerned with black print on white paper; however, any other combination of colors is more likely to give contrast problems than the black and white combination.

There is no form of room illumination which can be used in homes or industries or classrooms which actually causes damage to the vision of any person. The loss of sight is always due to some diseased state and is never influenced by the type or position of illumination. The only consideration

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

at present is one of *maximum* ocular comfort, and so long as the desk-level illumination approaches 25 f.-c. and the light is not directly in the faces of the students, any type of fixture which meets the above demand is satisfactory.

Therefore, it is possible to say that the unprotected light would be safe as far as ocular disease is concerned. Concerning the problem of glare, however, it is possible that some of the students, especially those in the back of a room looking forward, will, from the ocular standpoint, be bothered to some degree.

TRICHOMONIASIS IN MEN

To the Editor:—*What are the criteria for establishing a diagnosis of trichomonas infestation in a male patient, and what treatment, if any, is recommended? I have yet to find evidence proving the existence of such infestation in men, yet women have recurrences.*

Orin Q. Flint, M.D., Delhi, N. Y.

Answer.—The criteria for establishing a diagnosis of trichomoniasis in a man who is without symptoms (if the female partner is infested) is the finding of the trichomonads in (1) a centrifuged sample of morning urine or (2) the prostatic secretion obtained by prostatic manipulation. Sometimes trichomoniasis in a man clears spontaneously. If treatment is necessary, 500 mg. of chlortetracycline hydrochloride, given four times daily for a week, is commonly used. Prostatic massage is of no benefit.

The factors making it difficult to find the trichomonads in the male may be (1) inability to recognize them and (2) improper preparation of the specimen. It is suggested that a hanging drop be prepared, of either the centrifuged morning urine or the same with a drop of prostatic secretion, diluted with a drop or two of warm isotonic sodium chloride solution. If they are not found in one specimen, the procedure must be repeated; if they are present, they will be seen.

JAUNDICE

To the Editor:—*The symptoms of which diseases disappear when a person becomes jaundiced?*

Roy Overt Halloran, M.D., Charleston, W. Va.

Answer.—Jaundice per se does not cause improvement in clinical features of other diseases, although accumulation of bile pigments in the central nervous system is often associated with drowsiness and amelioration of subjective symptoms. A decrease in signs and symptoms of a nonrelated disease in the icteric person is usually due to associated liver failure. Thus, in jaundice of hepatic origin, an increase in circulating hydrocortisone incident to liver dysfunction may produce an amelioration of symptoms of rheumatoid arthritis, or cause temporary disappearance of psoriasis, eczema, and other chronic skin disorders. Nutritional or hormonal imbalance in the icteric subject with hepatic insufficiency is also frequently followed by a decrease in hypertension and its manifestations. On the other hand, clinical features may be made worse by liver dysfunction: disturbance in coagulation may initiate bleeding from a previously quiescent lesion and hormonal or enzymatic changes may result in an exacerbation of diabetes.

An increase in circulating free or conjugated bilirubin in the absence of liver failure usually causes an aggravation of symptoms of nonhepatic diseases. In obstructive jaundice one frequently notes exacerbation of skin lesions due to deposition of bile salts; aggravation of chronic renal disease as a result of biliuria; and development of constipation, steatorrhea, and gaseous eructation due to absence of intestinal bile.

INSOMNIA, SLEEP, AND DREAMS

To the Editor:—*In reading the American medical literature on the subject of insomnia, I have come across a classification of insomnia into types 1, 2, 3, and 4. I cannot find the exact meaning of this classification and would be most grateful if you could give me information on this matter.*

Medical Laboratories, England.

Answer.—In Sadler's "Practice in Psychiatry" (St. Louis, C. V. Mosby Company, 1953, pp. 934-935) there is reference to four types of sleep disorders to which the correspondent may be referring. It should be noted that among clinicians there is no general agreement on standard categories of sleep disorder. Each hospital or training center generally uses its own local categorizations, although many of them tend to follow the types described by Adolf Meyer and his pupils at the Henry Phipps Psychiatric Clinic and referred to in Diethelm's "Treatment in Psychiatry" (New York, the Macmillan Company, 1950).

Editors Note: Since there have been numerous inquiries about sleep and related subjects, it is worthwhile to list the other references sent by our consultant (the first three). Additional ones have been supplied by this office to cover the subject.

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OVARIAN CANCER AND CHEMOTHERAPY

To THE EDITOR:—*A 37-year-old woman underwent her first abdominal operation in 1954, when a large right ovarian cyst was removed and a biopsy performed on the left ovary. The histological diagnosis was benign follicular cyst of the right and left ovaries. Two years later the patient developed severe pain in the left lower quadrant, and the mass in her left ovary became large and tender. A total hysterectomy was performed, and the tumor that was removed was reported to be a papillary carcinoma of the ovary, with metastases to the omentum and the peritoneum. The patient received deep x-ray therapy. She was asymptomatic until May, 1959, when a large tumor mass was felt in the right lower quadrant. The mass was a recurrent carcinoma involving a large section of the omentum and the cecum. As much as possible of the carcinoma was removed, and deep x-ray therapy was repeated. She was given a course of therapy with triethylene thiophosphoramide by a consulting physician and has been taking this medicament since Sept. 17, 1959. Are any of the anticancer drugs effective against this type of tumor?*

D. T. Molloy, M.D., Malta, Mont.

ANSWER.—Few chemotherapeutic approaches are left to offer a woman who has progressive disease after two courses of deep x-ray therapy and six months of therapy with an alkylating agent. Changing to another alkylating agent probably would be of little help and might lead to severe bone marrow depression. A trial of cyclophosphamide in two-thirds of the usual dose might be effective and prove somewhat less toxic to the bone marrow. An antimetabolite of uracil, 5-fluorouracil, has been used by some investigators with varying effect in patients with inoperable carcinomas of the ovary. It is a highly toxic drug, and pancytopenia may result in those who have received prior intensive pelvic irradiation. Perfusion of the pelvis with chemotherapeutic agents such as mustards, antimetabolites, and actinomycin has been tried but requires an elaborate setup with extracorporeal circulations and pump oxygenators. The results to date are difficult to evaluate.

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GLAUCOMA AND ABDOMINAL PAIN

To THE EDITOR:—*A girl aged 17 years has been having severe pain in the right lower quadrant of her abdomen. She also has bilateral glaucoma and Ménière's syndrome (unilateral). The Ménière's syndrome has been well controlled medically although the glaucoma was not. Her abdominal pains seem to follow the episodes of intraocular tension. Bilateral operation was successful in relieving the increased ocular tension, and the abdominal pain likewise disappeared. Is the persistent abdominal pain described associated with uncontrolled glaucoma?*

Paul Guggenheim, M.D., Council Bluffs, Iowa.

ANSWER.—The systemic symptoms of acute closed-angle glaucoma include sweating, prostration, nausea, vomiting, shock, and the type of abdominal pain described. This consultant has seen a patient, treated for three days for acute cholecystitis, who had an acute glaucoma caused by a swollen cataract. This is not unique, and it is probable that the patient described had extremely narrow angles which closed from time to time. A sudden rise in tension would accompany each angle closure with resultant local, and, in this case, remote abdominal pain. Usually loss of vision, redness of the eyes, and severe headache are also present.

Another misleading factor in this case might be the patient's age. Acute glaucoma usually occurs after the age of 40 years, but it occasionally occurs in the third decade of life.

DRYNESS OF THE PALATE

To THE EDITOR:—*A 28-year-old man has been severely bothered by a persistent dryness and "drawing" of the palate of six months' duration. This began after he received penicillin for a sore throat. Numerous examinations by otolaryngologists have revealed no abnormalities. He has been told that this is a neurotic symptom and has been treated with sedatives and tranquilizers, with only slight transient improvement. I first saw him four months after the onset of the symptoms, at which time a complete physical examination was made. The only abnormality was slight atrophy of the mucosa of the soft palate, with moderate injection. Results of laboratory tests were all negative. Throat culture grew streptococci, diphtheroids, and Escherichia coli, but no fungi. My impression was that of a localized penicillin sensitivity, and I have tried to treat him with large doses of antihistamines and prednisone, with no effect. I have also tried a mouth wash of hydrocortisone, also without effect. What further treatment should be tried?*

M.D., Connecticut.

ANSWER.—The diagnosis of the symptoms described without objective findings on examination by competent physicians and specialists is most difficult. From the history, it would seem highly unlikely that the symptom was caused by hypersensitivity to penicillin. It is possible, however, that the previous infection of the throat resulted in the "slight atrophy of the mucosa of the soft palate" with the subjective sensation of dryness or drawing. It might be well to stop all medication for a time and follow the course of the symptoms. The patient should be encouraged to keep his mouth moist to prevent the symptom of dryness.

POSTOPERATIVE NEUROLOGICAL SENSATION

To the Editor:—*A 64-year-old man underwent a transurethral resection in October, 1958, and an aortic graft for intermittent claudication in November, 1958. A few days after the transurethral resection he complained of a drawing sensation in the scrotum. Despite the absence of pain, the sensation, which has become progressively more severe, is so annoying that patient is unable to sit still when working. He has had some claudication in recent months but is able to walk. Therapy with phenobarbital and several tranquilizing agents has been tried without obtaining significant relief. Injections of nylidrin hydrochloride and vitamin* B_{12} *have not relieved the paresthesias. Prostatic massages have been ineffectual. A urologist has infiltrated the spermatic cord and blocked the pudendal nerve with an anesthetic agent, with only equivocal alleviation of symptoms. A neurologist suggested that, since flexion of the thigh appeared to aggravate the sensation, some mechanical irritation of the nerves in the pelvis might produce the patient's symptoms. What is the cause of this intensely annoying symptom? What treatment will give relief so that the man can return to work?*

Robert O. Knox, M.D., Denver, Colo.

Answer.—The neurologist's opinion that some mechanical irritation of the nerves in the pelvis might produce the patient's symptoms is probably right. This can happen after an aortic graft operation. The transurethral resection of the prostate probably had little, if anything, to do with causing the symptoms. The treatment should be conservative and guided by periodic consultation with a vascular surgeon and a urologist.

CARDIAC DISEASE AND TRUMPET PLAYING

To the Editor:—*Should a 36-year-old physician who has a minimal degree of coronary insufficiency and possibly a small infarct continue his hobby of trumpet playing?*

M.D., Michigan.

Answer.—Advice to patients who have had a coronary thrombosis should include that they avoid exertion in which they have to hold their breath, set their chest muscles, and perform a Valsalva maneuver (i. e., pushing and shoveling), because such exertion can cause a marked decrease in blood flow due to damming of blood. The resultant slowed flow of blood through the coronaries could predispose to thrombosis in a narrowed vessel.

To a certain extent the same conditions would prevail in trumpet playing, but I am inclined to think that the physician could probably play his trumpet with safety, provided that there are no associated conditions, such as hypertension or diabetes, that the heart size is normal, that there is no angina on exertion, and that the electrocardiogram does not show S-T segment changes on exertion.

OCCUPATIONAL INJURY AND DISABILITY CLAIM

To the Editor:—*A 22-year-old man, who is a roofer, developed sudden pain and swelling in his right testis while at work. He was treated for epididymitis. Although the swelling subsided temporarily, it recurred six weeks later. He was maintained on medical treatment without improvement. Three months after the original "injury," orchiectomy revealed a pure seminoma. The patient has asked about the possibility of filing claim with the Industrial Commission of Ohio. What should be the advice of the physican?*

Gilbert H. Derian, M.D., Cleveland.

Answer.—Your question is most difficult to answer in specific terms. Some general principles can be stated as guide-posts in advising the patient.

An employee is entitled to compensation when he suffers an injury or contracts an occupational disease in the course of and arising out of his employment. It is not necessary that an employee receive some external violence for an injury to be accidental within the meaning of the Workmen's Compensation Act. When an employee in the performance of his work suffers sudden disability, an accidental injury is sustained even though the result would not have obtained had he been in normal health. If a worker's existing physical structure gives way under the stress of his labor, this is an accident which arises out of his employment. The applicant for compensation must present evidence that the injury arose from the employment, but he need not negate every possibility that the injury might have arisen other than out of the employment.

The Industrial Commission determines the facts. It makes these determinations by drawing reasonable inferences and conclusions from competent evidence, both direct and circumstantial. Since the Commission performs this function, it seems appropriate that the case referred to be brought before it.

ABSTRACTS FROM THE LITERATURE

A. M. A. Archives of Environmental Health

22:1-55 (July) 1960

Adhesion of Solid Particles to Solid Surfaces
M. C. Kordecki and C. Orr Jr. ....p. 1
Reticuloendothelial Response to Benzene
Z. T. Wirtschafter and M. G. Bischel....p. 10
Malignant Disease in African Gold Miners
C. B. Chatgidakis....p. 17
Roasted Chromite Ore in Production of Cancer
W. W. Payne....p. 20
Asbestosis and Carcinoma of the Lung
J. Anderson and F. A. Campagna....p. 27
Industrial Hygiene and Triphenyl Phosphate
W. L. Sutton, C. J. Terhaer, and others....p. 33
In Vitro Effects of Aliphatic Nitro Compounds
F. L. Estes and J. H. Gast....p. 47
Dermatoses from Phenylmercuric Salts
G. E. Morris....p. 53

Adhesion of Solid Particles to Solid Surfaces.—The adhesion of particles found in polluted atmospheres to typical construction materials was studied, as were effects of humidity upon the adhesion. Humidity-conditioned particles were sprinkled on a preconditioned solid surface, and the size distribution of the particles adhering was determined. Solid and adhering particles were then subjected to centrifugal force, tending to throw the particles off. Adhering particles were measured after centrifugations applied at successively higher speeds. The particles remaining, as speeds increased, were found to shift regularly toward smaller sizes. Calculations based on the experimental results indicate that winds and vibrations re-entrain little actual particle debris once it becomes attached to various surfaces. The effects of humidity were found to vary with the materials comprising the particles and surfaces.

Reticuloendothelial Response to Benzene.—The object of this study was to determine the cellular activity in the lymph node, thymus, liver, bone marrow, spleen, and peripheral blood of Long-Evans rats induced by a single subcutaneous injection of benzene. Cellular reaction differed as to intensity and duration in the imprints of organs examined, but all clearly showed that at 1 week, when the study was terminated, the hemopoietic system had not returned to normal. A marked increase of reticuloendothelial cells of pulp-cell type were observed in splenic imprints. In bone marrow, reticuloendothelial response reached a peak at 72 hours, and foreign-body type giant cells were observed. Decreased thrombocyte formation was present in the megakaryocytes. Reticuloendothelial cells of macrophage type were increased in the lymph node and thymus.

Malignant Disease in African Gold Miners.—The object of this autopsy survey was to investigate the incidence of malignant disease in this group of African male gold miners, with particular reference to primary carcinoma of the lung. The incidence of malignant disease was found to be 6.3% and primary carcinoma of the liver was the commonest malignancy (72%). The incidence of primary carcinoma of the lung was low (0.3%) and comprised 4% of all malignancies. To determine whether underground service in the gold mines on the Rand and in the Free State increased the incidence of primary carcinoma of the lung, 691 African silicotic patients were also examined. Not 1 case of primary carcinoma of the lung was detected in these patients.

Role of Roasted Chromite Ore in Production of Cancer.—Residue from the leaching of roasted chromite ore was fractionated according to particle size and tested in mice for carcinogenicity. The smaller particles contain a higher percentage of hexavalent chromium than the larger particles. The subcutaneous injection of 3,4-benzpyrene with the residue resulted in a lower incidence of tumors than when the benzpyrene was injected alone or with insoluble chromic phosphate. When implanted with sheep fat and without benzpyrene the residue produced sarcomas in 4 of 70 rats. A fraction of the residue containing little water soluble chromium produced tumors in 3 of 52 mice. No tumors occurred in the control groups. The results give additional evidence that the intermediate products in the production of chromium chemicals and the discarded residue may be hazardous.

Industrial Hygiene and Triphenyl Phosphate.—There exists the possibility that the manufacture of triphenyl phosphate (TPP) may present significant occupational hazards. For this reason, the animal toxicity of TPP was reinvestigated, and the manufacturing process was maintained under close industrial hygiene and medical observation. TPP exhibited low acute toxicity in rats, mice, and guinea pigs. It did produce delayed generalized illness with paralysis when administered to cats. The acute toxicity of TPP was found to be approximately equivalent to triorthotolyl phosphate (TOTP) in rats, mice, cats, and monkeys but much less toxic than TOTP in guinea pigs, rabbits, and chickens. There was poor absorption from the gastrointestinal tract, subcutaneous tissue, and skin. Skin application caused no irritation. It produced cholinesterase inhibition both in vitro and in vivo. However, it was not a sufficiently potent active anticholinesterase agent to cause cholinergic symptoms in animals given large doses. Repeated medical examination did not reveal any evidence of adverse clinical effects in men exposed for as long as 10 years to TPP vapor, mist, and dust at weighted average air concentrations of approximately 3.5 mg. per cubic meter. A statistically significant reduction in red blood cell cholinesterase activity (but not plasma cholinesterase activity) was found in the group of men regularly engaged in the manufacture of TPP. This probably represents an effect of TPP absorption but further experience is necessary to confirm this. There have been no relevant nervous-system symptoms or findings during the 10-year period of observation. It was concluded that the manufacture and use of TPP does not present a serious industrial hazard.

The place of publication of the periodical appears in brackets preceding each abstract.

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The in Vitro Effects of Aliphatic Nitro Compounds.—The shorter chain nitro compounds give indication of being effective inhibitors of tissue respiration. At low concentrations saturated (C_1-C_3) and unsaturated (C_3) alkyl nitro compounds inhibit the oxygen consumption of polymorphonuclear leucocytes as well as homogenates of heart and liver. When the concentration of tissue is held constant, the oxygen consumption passes through a minimum and increases with the concentration of nitro compound. For 2-nitropropane with heart homogenates maximum inhibition represents a molar concentration to tissue nitrogen ratio of 5:1. These observations are interpreted as indicating that more than 1 reaction is occuring. At the concentration involved neither nitrite nor nitrate ions have any effect on the tissues used. Clarification of these observations is complicated by the general chemical behavior of these compounds. It is possible that 1 of the reactions is auto-oxidation of the nitro compounds.

Dermatoses from Phenylmercuric Salts.—Phenylmercuric salts in their pure state and in relatively high concentrations may cause blistering of the human skin, or they may act as primary skin irritants or allergens. Although their use in herbicides, in agricultural fungicides, in industrial germicides, in nasal and contraceptive jellies, and, in very dilute concentration, as a primary antiseptic has been stated to be without danger to the public, Dr. Morris has reported 3 cases of dermatoses directly attributable to them. Two of these cases were due to phenylmercuric nitrate—in a crabgrass killer and in a skin ointment—while phenylmercuric acetate, used as an ingredient in a contraceptive jelly, caused the 3rd case.

A. M. A. Archives of General Psychiatry

3:1-110 (July) 1960

Does Time Stand Still for Some Psychotics?
O. F. Ehrentheil and P. B. Jenney. ....p. 1
Sedation and Tranquilization
G. L. Klerman and others. ....p. 4
The Methacholine Test in Depressive States
B. M. Davies. ....p. 14
Correction of Deviant Responses in Word Association Test
W. Weintraub and others. ....p. 17
Observations on Adopted Children
M. D. Schechter. ....p. 21
Psychiatric Patients Following Sensory Deprivation
R. G. Gibby and others. ....p. 33
Organic Integrity Test (O. I. T.)
H. C. Tien. ....p. 43
Dominance Behavior in the Rat
T. C. Mezei and J. Rosen. ....p. 53
Use of Home Visits for Psychiatric Evaluation
D. A. Schwartz, R. Waldron, and C. W. Tidd. ....p. 57
The Autistic Child
H. H. Eveloff. ....p. 66
Problems in Contemporary Psychoanalytic Training
T. S. Szasz. ....p. 82
Benign Auditory and Visual Hallucinations
G. R. Forrer. ....p. 95
Physiology and Psychosomatic Medicine
H. Schaefer. ....p. 99

Asbestosis and Primary Carcinoma of the Lung.—This is a case report of asbestosis associated with primary carcinoma of the lung and a review of the literature. It is the 23rd such case reported with complete autopsy findings. The patient had a 30-year exposure to asbestos and had also been a very heavy smoker. Thoracotomy with attempted biopsy of a hilar mass was unsuccessful due to severe adhesive pleuritis. At autopsy, widespread carcinomatosis was found, associated with the asbestosis granulomata. The primary lesion was on the right lower lobe or middle lobe of the lung. Factors such as the relation of asbestos and nonspecific irritants to carcinoma, the factor of smoking, and the site of origin of the neoplastic lesion in relation to the portion of the lung most affected by asbestosis are discussed.

Does Time Stand Still for Some Psychotics?—Thirty elderly schizophrenic patients who had been hospitalized for 30 years were asked the simple question, "How old are you?" Nine were totally inaccessible. Seven of the remaining 21 patients gave as their ages approximately that which they had at the onset of their disease. Ten patients with dementia paralytica and 10 epileptics were used as controls. Only one of these gave as his age that at the onset of his psychosis. The answers given by some chronic schizophrenics suggest that for them time was indeed standing still. This is of interest in view of the studies on the meaning of time in current philosophy and psychiatry. We referred, in the discussion of our findings, to some psychoanalytic and existentialist articles which deal with the meaning of time to psychologically disturbed people.

Sedation and Tranquilization.—Clinical experience with the capacities of the newer psychopharmacological agents to alter emotional states and influence psychopathological processes has generated the concept of tranquilization. This concept implies that these drugs induce a psychological and physiological state qualitatively different from that induced by previously available "sedative" drugs. Three psychopharmacological agents, a tranquilizer (meprobamate), an antihistaminic sedative (phenyltoloxamine), and a barbiturate sedative-hypnotic (secobarbital) were assessed in normal human subjects. Using a double-blind design, each drug was studied at 2 dosage levels and also compared with a placebo. The effects of a single oral dose were observed on a number of parameters including (1) physiological functions; (2) level of consciousness and alertness; (3) psychomotor performance; (4) mental functioning; (5) subjective effects; (6) behavior during psychiatric interviews. The data from this study suggest that sedation and tranquilization are similar states. It was concluded that the special properties of so-called tranquilizer drugs do not lie so much in their ability to induce a unique psychic state different from sedation, but lie in the dosage margins between their sedative effects and their differential effects upon alertness, psychomotor performance, mental functioning, and physiological functions. The classic model of the polarity of depression-stimulation action upon central nervous system functioning should be modified in favor of a multidimensional model for psychopharmacological action.

Methacholine Test in Depressive States.—The hypothesis that clinical improvement in hospitalized patients with depressive illnesses is associated with a change in their blood pressure response to methacholine was tested. One observer performed the methacholine test in 25 consecutive women patients in whom diagnosis of a primary depressive illness was made. The test was first done soon after admission, and the degree of depression rated clinically on a simple rating scale. Just prior to discharge from hospital, when the patient was free from depressive symptoms, the test was repeated by the same observer in a similar setting. The 25 patients had an average age of 43 years, and remained in hospital for an average of 10 weeks. Treatment was not influenced by test results, 24 of the patients receiving shock therapy (E. C. T.) either alone or with antidepressant drugs. The difference between the correlated means of the basal systolic blood pressure, the maximal drop of systolic B. P., and the time taken for the systolic B. P. to return and stay at the basal level were calculated. In each instance no significant difference was found; the results do not support the hypothesis that was tested.

The conclusion that any significant alteration in a patient's psychological state is accompanied by a change in his psychological response to the test was not confirmed by this investigation, though it is pointed out that the systolic B. P. alone is not a true index of total autonomic activity.

Some Observations on Adopted Children.—In a 5-year period, 120 children were seen in a psychiatric practice. Of these, 16 were adopted children. This is a much higher percentage than is found in the general population. In all the children, irrespective of when adopted, the fact of adoption seemed to play a cardinal role in the development and continuation of specific emotional problems. Adoptive parents and their attitudes contributed greatly, but there was a feeling of being different and impermanent which suggested that the adopted child is more prone to emotional difficulties than the nonadopted. There is evidence that telling about adoption during the oedipal phase may be condusive to neurotic results.

Psychiatric Patients Following Sensory Deprivation.—The major purpose of our study was to investigate behavioral changes in psychiatric patients following relatively brief sensory and social deprivation under mild experimental conditions. Subjects showed significant reduction in the severity of symptoms following the experience. Positive behavioral changes significantly outnumbered the negative ones. Further, the positive changes tended to be enduring while the negative changes tended to be transitory. The disruptive effects on mental functioning were of limited extent, unlike those reported by other investigators using more prolonged and drastic conditions. There was in general an increased desire for social contacts and therapeutic interactions with the staff. The subjects showed a greater awareness of their inner problems, and a less rigid utilization of repressive and inhibitory defenses. Techniques of sensory deprivation may ultimately prove to have many psychotherapeutic possibilities.

Dominance Behavior in the Rat.—The purpose of this investigation was to determine the effects of infantile stimulation in the form of gentling on social dominance in rats. Fourteen male albino rats were stroked 5 minutes daily from age 13 to 25 days. From 47 to 60 days of age, there were 196 different feeding competitions in which every gentled rat was paired once against every ungentled rat. The gentled rats were more dominant than the ungentled controls, as indicated by the significantly greater number of competitions won. These differences in dominance behavior were also found to persist into the later life of the animals. It was suggested that gentled rats were less emotionally reactive during the feeding competitions and hence less inhibited in their fighting behavior than the ungentled subjects.

Use of Home Visits for Psychiatric Evaluation.—Recent reports in this country and abroad indicate the value of home visits for evaluation and treatment of psychiatric patients. Home-visit psychiatric evaluations were included in the psychiatric residency program at the University of California, Los Angeles, (UCLA) in 1958. This was partly to investigate their clinical value, but it was also used as a teaching device. Ten patients referred to the UCLA Psychiatric Inpatient Service were seen for home evaluations in 1958 and 1959. One patient was seen privately for home evaluation by 1 of the authors. Six of the 11 visits provided information which would not have been obtained in office evaluation and which was important in making recommendations or planning treatment. The other 5 visits were clinically interesting but provided no obvious advantages over office evaluation. Aside from clinical aspects, home visits were considered extremely valuable from a teaching viewpoint.

The Autistic Child.—Increasing interest is being focused on the intriguing psychoses of childhood. In 1943 Dr. Leo Kanner called attention to a a group of children with a marked disturbance of affective contact which, he felt, could be differentiated from other severe non-neurotic childhood disorders. In this and subsequent papers he and others further described a relatively uncommon psychotic illness which had the classical triad of inception in the first one-half to 1 year of life, insistence on sameness, and extreme isolation with respect to human contact but not to inanimate objects. The new syndrome was named Early Infantile Autism. In this paper this illness is discussed in the following categories: signs and symptoms; differential diagnosis; case history of a 3½ year old girl freely illustrated with raw data; rationale of treatment; psychodynamic etiologic formulation; prognosis.

Problems in Contemporary Psychoanalytic Training.—This article presents an analysis of: (1) the relationship between psychoanalysis and medicine; (2) the psychoanalytic pledge; (3) the training analysis. The discrepancies between scientific considerations and organizational and training policies were noted. The main conclusions and recommendations were as follows. (1) To define psychoanalysis as a special branch of medicine is scientifically unsatisfactory. Pyschoanalysis is 1 among the sciences concerned with the study and alteration of human behavior. (2) The psychoanalyst's pledge is morally offensive and should be abolished. (3) The training analyst's double role—as therapist for the candidate and as guardian of psychoanalytic standards and loyalties for his organizations (institutes, societies)—is incompatible with the proper conduct of the psychoanalytic procedure. The structure of the training analysis, as presently conceived, interferes both with the candidate's personal analysis and his learning how to analyze.

Benign Auditory and Visual Hallucinations.—Hallucinations, traditionally accepted as diagnostic criteria of psychosis, are shown in fact to be common-place experiences of everyday life. The ego's response to the phenomena, rather than the mere presence of hallucinations, determines whether or not the perceiver is psychotic. Hallucinations are experienced by normal people with the approximate frequency of parapraxes under circumstances of affective or actual hunger. Analysis of examples supports psychoanalytic theory that, irrespective of ideational content, the hallucinated perception serves to fill for the subject what would otherwise be a painful void. The sensory perceptive apparatus through which the hallucination is perceived has the dual unconscious representation of maternal breast and infantile mouth.

The hallucinated perception itself has the unconscious symbolic meaning of the flow of milk from the former to the latter.

A. M. A. Archives of Internal Medicine

106:10-96 (July) 1960

Nodular Goiter
R. P. Stoffer, J. W. Welch, and Others. ....p. 10
New Aspects of Thyroid Therapy
H. Zondek, H. E. Leszynsky, and G. W. Zondek. ....p. 15
Record of Medical History
C. E. Forkner. ....p. 22
Notes on Vascular Spiders in Healthy Persons
W. B. Bean. ....p. 35
Diseases in a Mission Hospital in Northwest India
F. G. Scovel. ....p. 39
Phosphate Excretion Tests and Hyperparathyroidism
T. B. Reynolds, H. Lanman, and N. Tupikova. ....p. 48
Chlorothiazide Tagged with Radioactive Carbon (C^{14})
H. R. Brettell, J. K. Aikawa, and others. ....p. 57
Familial Sarcoidosis
R. K. Merchant and J. P. Utz. ....p. 64
Postnecrotic Cirrhosis
A. S. Weissbein and N. M. Scott Jr. ....p. 71
A Study of Antihypertensive Agents
Veterans Administration Cooperative Study. ....p. 81

Nodular Goiter.—The incidence of palpable nodular goiter in Kansas is 7%. Cancer was diagnosed preoperatively in only 29 of 206 cases. The distinction by palpation of multinodular and uninodular goiters was correct in only 56% of our cases. Twenty years after introduction of iodized salt a relative increase in cancer cases of from 7 to 13% was noted. Furthermore, the death rate from thyroid cancer as reported by the Kansas State Board of Health has doubled during the last 20 years. Thyroid extract and radioiodine were ineffective in treating nontoxic nodular goiter. Before a clinical diagnosis of cancer can be made, the treatment of choice for nodular goiter is still thyroidectomy if the patient is a good surgical risk.

New Aspects of Thyroid Therapy.—The effects of unphysiologically large quantities of thyroid substances (90 mg. triiodothyroacetic acid or equivalent doses of desiccated thyroid) given within 6 to 10 days were investigated in 2 patients, each with primary and secondary myxedema, and in 3 siblings with sporadic goitrous cretinism, presumably due to a genetically transmitted inability of the thyroid to bind the trapped iodide. (Thyroid autoantibodies were not detected in the serum.) Massive-dose therapy (stosstherapy) was effective only in the goitrous cretins in whose thyroids a normal function [normal or elevated radioactive iodine (I^{131}) uptake, normal serum nonradioactive isotope of protein bound iodine (PBI^{127})] lasting 6 to 7 months was thus induced, the patients remaining euthyroid and more or less agoitrous during the same length of time. It was concluded that in thyroid deficiency due to intracellular enzymatic defects (biochemical myxedema), massive-dose therapy may temporarily normalize hormone synthesis, presumably by activation of the defective enzyme.

Notes on Vascular Spiders in Healthy Persons.—Observations made on normal subjects in the spring and summer of 1940, 1941, and 1942 reveal that approximately 10% had vascular spiders. Follow-up in the fall of 1959 revealed no change in some of these patients; others had lost 1, a few, or all lesions, and some others had developed new ones. These findings, together with observations on hereditary hemorrhagic telangiectasia, in which lesions may come and go, illustrate the secular trend which may occur in lesions of the skin where, presumably, small blood vessels are being formed and being destroyed over long periods of time.

Diseases in a Mission Hospital in Northwest India.—An analysis of diagnoses on 48,429 inpatients showed an increasing incidence of degenerative diseases correlative with a longer life expectancy. Sequellae of cerebral and cardiovascular accidents were frequently encountered. Is this related to a diet of buffalo milk rich in unsaturated fatty acids? Middle class obesity was common, often with mild diabetes. All forms of tuberculosis were prevalent, especially intestinal and peritoneal tuberculosis. Patients with leprosy, usually inactive, live in communities, and many of these had pulmonary tuberculosis. Tertian malaria was endemic. Both bacillary and amebic dysentery were constantly seen during the long hot months. Hypoproteinemia and iron-deficiency anemia were almost universally present in the poorer patients, often augmented by hookworm infestation and frequent gestations. Some patients also presented megaloblastic anemia. Carcinoma of the cervix occurred in 1,164 patients and abortion or miscarriage in 2,222.

Phosphate Excretion Tests and Hyperparathyroidism.—Tests of phosphate excretion were performed in 14 patients with hyperparathyroidism and compared with results in a group of 32 control subjects with normal serum calcium and phosphate values. All of the 14 hyperparathyroid patients had hypercalcemia, and 11 had low serum phosphate levels. None had significant renal impairment. Values for tubular reabsorption of phosphate (4-hour forenoon period) overlapped considerably between the 2 groups. Six of the 14 hyperparathyroid patients had values above 80%; the range was 50 to 87% (mean, 74%). Phosphate clearance (4-hour forenoon period) ranged from 9.3 to 28.0 cc. per minute (mean, 17.1 cc. per minute) in the hyperparathyroid patients and from 4.3 to 21.0 cc. per minute (mean, 11.5 cc. per minute) in the control subjects. It was concluded that other factors, in addition to parathyroid activity, may influence renal tubular handling of phosphate, and that failure to control these factors limits the diagnostic usefulness of phosphate-excretion tests.

Chlorothiazide Tagged with Radioactive Carbon (C^{14}).—Chlorothiazide labeled with C^{14} was given orally or intravenously to 30 subjects; serial blood and urine specimens were analyzed for radioactivity. All of the radioactivity injected intravenously into 3 normal subjects was recovered in the urine within 24 hours; 33 to 58% of the dose given orally to 7 normal subjects was so recovered. Renal excretion of radioactivity was lower in patients with congestive failure, renal glomerular disease, and hepatic disorders. Patients with liver disease showed the poorest diuretic response to chlorothiazide and the lowest serum concentrations of the drug. Excretion of radioactivity was in inverse ratio to the severity of diseases affecting the heart, kidneys, or liver, but the factors responsible for this uniformly poor response may vary with different pathologic conditions.

Familial Sarcoidosis.—Sarcoidosis has been observed in a mother and her daughter. The criteria for this diagnosis included (1) a compatible clinical picture, (2) granulomatous inflammation with little or no necrosis and the absence of demonstrable micro-organisms in specially stained sections of biopsy material, (3) negative cultures (particularly for acid-fast bacteria and fungi) of appropriate body fluids, exudates, and surgically excised granulomatous tissue, and

(4) a positive Kveim test. These cases of sarcoidosis and an additional 73 others involving more than one member of each of 32 families suggest the possibility that a complex hereditary trait is operative in the pathogenesis of sarcoidosis.

Postnecrotic Cirrhosis.—Twenty-two consecutive patients, with a final diagnosis of histologically proven postnecrotic cirrhosis, were studied in an effort to determine the presenting clinical characteristics and the relationship to past episodes of recognizable liver disease. In only 6 was there an acceptable past history of acute infectious hepatitis. Sixteen patients had no background of factors, whether toxic, infectious, or nutritional, to which the final pathologic process could be attributed. The initial presenting complaints included such advanced complications of cirrhosis as ascites (4 cases), hepatoma (2 cases), and hemorrhage from esophageal varices (5 cases). Three patients presented with asymptomatic jaundice and 5 with hepatomegaly or splenomegaly, or both. It was concluded that although infectious hepatitis, including anicteric forms, may be an important etiological factor in some cases of postnecrotic cirrhosis, the majority of cases probably arise from as yet undiscovered causes.

A Study of Antihypertensive Agents.—In a double-blind control study of 198 hypertensive patients followed for 3 months to 1 year, the following results were obtained. In mild hypertension, reserpine (0.5 mg. daily maintenance dose) plus hydralazine (200 mg. per day) was more effective in reducing blood pressure than reserpine alone or placebos; in moderately severe hypertension, the reserpine-hydralazine regimen produced a mean decrease of 13.7 mm. Hg diastolic pressure as compared to minus 4.3 mm. with reserpine alone and plus 0.9 mm. Hg with placebos. The effects of ganglion-blocking agents plus reserpine were evaluated in a similar manner in 128 patients with severe and moderately severe hypertension. The mean reduction from hospital control levels was from 16.5 to 13.9 mm. Hg. There were no significant differences in antihypertensive effectiveness between mecamylamine, chlorisondamine, or pentolinium tartrate. In the moderately severe group, reserpine-hydralazine produced as great a reduction in diastolic pressure as reserpine-ganglion-blocking agents.

American Journal of Digestive Diseases, New York

5:175-282 (March) 1960. Partial Index

Biopsy of Normal Human Intestine
E. Strosselli .... p. 175
Locating Site of Intestinal Bleeding
W. H. Crosby Jr. and others .... p. 213
Serum Leucine Aminopeptidase in Carcinoma of Pancreas
J. B. Hammond, B. D. Rosenak and E. C. Khoo .... p. 233
Carcinoma of the Stomach
W. F. Mitty, L. M. Rousselot and W. J. Grace .... p. 249
Carcinoma of the Pylorus Simulating Benign Obstruction
C. H. Brown .... p. 264

Carcinoma of the Stomach.—The authors report on 169 patients with cancer of the stomach seen at a New York hospital between 1947 and 1955. Primary treatment was given to 155 of these patients, and follow-up was complete in 98.8%. Of the 155 patients 85% (132) were operated on. An exploratory laparotomy only was performed in 28%, a palliative gastroenterostomy in 15%, a palliative gastric resection in 10%, and a curative resection in 32%. The duration of symptoms seemed of little prognostic importance. The 5-year survival rate was 5.5% after total gastrectomies but was 34.4% after curative subtotal gastrectomy. As regards nutrition, patients who have undergone subtotal gastrectomy fared better than those who had undergone a total gastrectomy. The authors recommend that, wherever possible, an extended subtotal gastrectomy be performed rather than a total gastric resection. In patients who were still free from cancerous invasion of the lymph nodes, the 5-year survival rate, after curative subtotal gastrectomy, was 38%. The over-all 5-year survival rate in the 155 patients was 7.7%.

American J. Obstetrics & Gynecology, St. Louis

79:432-624 (March) 1960. Partial Index

Bacterial Flora in Vaginitis
B. C. Butler and J. W. Beakley .... p. 432
Paget's Disease of the Vulva
R. H. Kaufmann, E. H. Boice, and W. R. Knight .... p. 451
Basal Cell and Basal-Squamous Cell Carcinomas of Vulva
S. L. Marcus .... p. 461
Enzymatic Debridement of Cervical Erosions
E. A. Friedman and others .... p. 474
Genital Tuberculosis in Women
A. M. Sutherland .... p. 486
The X-Ray Diagnosis of Gas Gangrene of the Uterus
G. A. Doehner and others .... p. 542
Pathogenesis of ABO Hemolytic Disease
A. S. Wiener, V. J. Freda, and others .... p. 567

Bacterial Flora in Vaginitis.—Pure cultures of a special strain of Döderlein bacillus obtained from a normal 16-year-old girl were applied in 165 patients with vaginitis. The study was divided into 2 parts. Plan A was carried out on 135 patients during a 6-month period. The results in 111 were evaluated after the patients had been treated for 2½ months with vaginal applications of a skim-milk Döderlein bacillus preparation. The contents of a culture tube were poured into the vagina and a tampon was inserted. This was removed 5 or 6 hours later. Twenty-five patients with monilia vaginitis also received myocostatin vaginal suppositories. Their symptoms cleared rapidly and the vaginal flora became predominantly Döderlein bacilli. Nineteen patients with nonspecific vaginitis were treated intensively with pure cultures of Döderlein bacillus only. Eighteen of them were cured and their vaginal flora became predominantly Döderlein bacilli. Seventeen patients had trichomonas vaginitis and none of these had Döderlein bacilli in the vaginal flora. They were initially treated with pentavalent arsenical as well as with bacilli cultures. The arsenical therapy was discontinued and further applications of Döderlein bacilli resulted in a nearly predominant growth of this micro-organism. Sixty-five patients were treated under Plan B, including some who were continued from plan A. These patients received applications of a reconstituted lyophilized Döderlein preparation, with results similar to those obtained with the skim-milk preparation. The authors believe that the widespread use of systemic and local drugs destroys the proper vaginal biological balance and they advise that this balance should be restored or maintained with applications of pure cultures of a special strain of Döderlein bacillus.

Pathogenesis of ABO Hemolytic Disease.—In a 15-year study of 51 families in which ABO hemolytic disease had occurred, blood specimens taken from the affected child, from all available siblings, and from the parents were tested for ABO groups and for Rh-Hr types. Mothers of affected babies, with 1 exception, were group O, while the distribution of ABO group among fathers was similar to that in the general population. Babies with jaundice (74) were either group A or B. Of 35 normal children born before the first affected child, 11 were group A, while 7 normal children born after the 1st affected child were group O. The incidence of secretors and nonsecretors among the group-O mothers was similar to that in the general population, while the incidence of nonsecretors among the affected babies, their siblings, and their fathers was lower than in the general population. Apparently there are 2 main patterns of ABO hemolytic disease: one in which the maternal isoantibodies are mainly of heteroimmune origin and the first-born incompatible baby is generally affected; another in which 1 or more normal babies may 1st be born who are secretors and sensitize the mothers, so that subsequently born children develop typical erythroblastosis. The importance of recognizing ABO hemolytic disease lies in the possibility of treating the affected children and of having a prognostic evaluation of the outcome in future pregnancies.

Am. J. Tropical Medicine & Hygiene, Baltimore

9:105-227 (March) 1960

Trachoma: Strains of Elementary Bodies
E. S. Murray and others ....p. 116
Gastrointestinal Lesion in Asiatic Cholera
E. J. Gangarosa and others ....p. 125
Phycomycosis (Mucormycosis) in Indonesia
L. K. Joe ....p. 143
Humatin in Intestinal Amebiasis
S. Bell and A. W. Woodruff ....p. 155

Trachoma: Strains of Elementary Bodies.—An attempt was made to isolate strains of elementary bodies from 44 children between the ages of 4 months and 7 years who were suffering from trachoma. Thirty-nine of these children were residents of eastern Saudi Arabia and 5 lived in Egypt. The authors inoculated the yolk sacs of chick embryos. Nineteen strains were obtained in 45 attempts. Conjunctival scrapings were used from children who were shown to have typical inclusions at the time of the scraping. Nine of these strains were subjected to a series of tests which revealed that the strains were indistinguishable morphologically from the elementary bodies of the psittacosis-lymphogranuloma group of viruses. They were not sensitive to streptomycin and were free of other viruses and of pleuropneumonia-like organisms. They were toxic to white mice when administered by the intravenous route. They contained the heat-stable antigen which is common to the psittacosis-lymphogranuloma group of viruses. Viability of the trachoma elementary bodies in conjunctival scrapings persisted at a temperature of —60 C for many months if the specimens were stored in a medium containing sucrose, glutamate, and phosphate. One of the strains induced conjunctivitis in a chimpanzee, whose conjunctival cells showed typical inclusions at the height of the conjunctival reaction. A laboratory worker contracted severe trachoma, probably as a consequence of air-borne droplets arising from manipulations of concentrated suspensions of the elementary bodies. The reported data constitute a confirmation of the view held by other workers that elementary bodies, which have been propagated in yolk sac of the chick embryo, can induce clinical trachoma in man, and that the organisms can again be recovered in laboratory passage. It is not possible, however, to justify an assertion that clinical trachoma is a disease

American Rev. Respiratory Diseases, New York

81:315-480 (March) 1960. Partial Index

Study of Nodular Pulmonary Granulomas
J. B. Hutcheson and V. R. Waldorf ....p. 340
Pyrazinamide and Isoniazid in Pulmonary Tuberculosis
J. H. Matthews ....p. 348
Pleural Biopsy and Decortication as a Diagnostic Tool
D. E. Thomas and J. H. Anderson ....p. 352
Determination of Isoniazid in Body Fluids
Q. C. Belles and M. L. Littleman ....p. 364
Paper Electrophoretic Separation of Antituberculous Drugs
J. R. Maher and J. D. Hansen ....p. 373
Isoniazid and PAS With or Without Streptomycin in Tuberculosis
S. J. Berte and C. D. Bowen ....p. 407
Reduction of Chronicity of Tuberculosis by Prednisone
P. K. Bornstein and others ....p. 421
Egg-Yolk Dialysate for Mycobacterium Tuberculosis
J. O. Norman and R. P. Williams ....p. 423

Pleural Biopsy and Decortication as a Diagnostic Tool.—At Valley Forge Army Hospital, Phoenixville, Pa., it has been policy recently to perform a pleural biopsy in all cases of pleural effusion not diagnosed by other means, including needle biopsy of the pleura. Some of the patients had received antituberculosis therapy on the basis of a positive tuberculin reaction prior to arrival. Fifteen pleural biopsies have been performed. Six of these have revealed a granulomatous process compatible with tuberculosis. Mycobacterium tuberculosis was isolated in 5 of the patients by culture or by guinea pig inoculation. The remaining 9 patients were found to have chronic nonspecific pleuritis on the basis of the pleural biopsy. These 9 patients included persons who had never been treated, as well as some who had received up to 9 months of antituberculosis therapy. The 3 patients who underwent decortications for what was believed to be organized tuberculous pleural effusion were found to have other lesions, namely, metastatic carcinoma, Staphylococcus aureus empyema, and trapped lung secondary to spontaneous pneumothorax. The authors conclude that it is obligatory to perform a pleural biopsy by limited thoracotomy if lesser measures, including culture of fluid obtained by thoracentesis or needle biopsy of the pleura, fail to yield an etiological diagnosis in patients with pleural effusion.

Annales paediatrici, Basel

194:1-64 (Jan.) 1960. Partial Index

Epidemic of Interstitial and Suppurative Pneumonia
K. Astor and K. Schreier ....p. 1
Von Willebrand's Disease: Cause of Prolonged Bleeding Time
S. Van Creveld and others ....p. 37
Sodium Gluconate for Hyperbilirubinemia in Newborn Infants
H. J. Kaufmann and others ....p. 46

Epidemic of Interstitial and Suppurative Pneumonia.—While both interstitial pneumonia and staphylococcic pneumonia are observed in epidemics, little is known about the combination of these 2 forms of pneumonia. The authors report observations made on 18 infants, many of whom had signs of both forms of pneumonia. They explain the symptoms and course of the combined form on the basis of the history of a 10-week-old girl who died, and on whom autopsy was performed. The clinical examination indicated a suppurative pneumonia, but an interstitial pneumonia with the presence of plasma cells could not be ruled out. The condition of the child deteriorated despite intensive treatment. Death followed. Autopsy revealed an extensive, partly interstitial pneumonia, signs of increased plasma cell reaction, pulmonary emphysema, hypertrophy of the left ventricle, and hyperemia of the internal organs. The epidemic began in the maternity and nursing home with the illness of an infant in whom interstitial pneumonia was verified on autopsy. In other children, although the clinical course indicated that the pneumonia was interstitial, roentgenoscopy revealed infiltrations, and autopsy corroborated the diagnosis of the mixed form of pneumonia.

Cancer, Philadelphia

13:250-432 (March-April) 1960. Partial Index

Environmental Agents in Pathogenesis of Lung Cancer
P. Kotin and H. L. Falk ....p. 250
Pseudoadamantine Adenocarcinoma of Submaxillary Gland
I. Meyer and G. Shklar ....p. 270
Artificial Kidney in Lymphoma and Leukemia
J. Firmat and others ....p. 276
Amylase Activity in Pleural Effusions and Ascites
N. Ende ....p. 283
Hepatic Fibrosis in Leukemia: Complication of Therapy
R. V. P. Hutter and others ....p. 288
Primary Hemangiopericytoma of Bone: Case with Metastases
R. A. Marcial-Rojas ....p. 308
Carcinoma of the Lung
L. G. Jacobs, J. Yee, and I. A. May ....p. 362
Unsuspected Carcinoma in Suprapubic Specimens
W. C. Bauer and others ....p. 370

Carcinoma of the Lung.—The records of 321 patients with carcinoma of the lung were studied statistically. The dependent variable, survival, was measured to the nearest whole month and calculated from the day of entry to the hospital to the day of death. In the case of survivors it was measured to the cutoff date. The independent variables were age, clinical stage, pathological diagnosis of cell type, initial length of symptoms, type of surgical treatment, and amount of irradiation therapy. The rate of "cure" (absence of symptoms) was approximately 8% at 2 years, 7% at 5 years, and 5% at 7 years. The cure rate was 14% in the patients with peripheral pulmonary carcinoma and 2.5% in those with carcinoma located centrally. The multiple correlation analysis showed that patients in whom curative surgery was possible and was performed lived longer by a factor of about 4, and those receiving irradiation therapy lived longer by a factor of about 2 when given an adequate depth dose (more than 4,500 r). The survival table showed that only 1 patient in the untreated group and 31 patients in the treated group survived for more than 1 year. The survival rate was 22.5% in the treated and 0.5% in the untreated group. The multiple correlation analysis confirmed findings obtained from the survival tables. The authors interpret the results as demonstrating that some new method of approach is the only hope for better results.

Unsuspected Carcinoma in Suprapubic Specimens.—Fifty-five cases of unsuspected carcinoma were found in 847 suprapubic prostatectomy specimens. The mean age of the patients who underwent suprapubic prostatectomy was 67.8 years. The mean age of those with prostatic carcinoma was 71.3 years, a statistically significant difference. Eight patients were treated by orchiectomy only; 41 were treated with diethylstilbestrol (Stilbestrol) only; 12 received diethylstilbestrol after orchiectomy; 2 received x-ray therapy postoperatively. Nineteen patients received no antiandrogenic treatment. With 1 exception, the patients who died of carcinoma had received some type of antiandrogenic therapy, while half of the patients with a favorable outcome had neither received estrogens nor undergone orchiectomy. The 55 patients were followed up for a minimum of 5 years. Six groups of patients were analyzed: those living and well (14); living with evidence of cancer (1); dead of other causes (9); dead of other causes, with evidence of cancer (3); dead of other causes, with unknown status of cancer (9); dead of prostate cancer (16); and postoperative deaths (3). The survival curves showed an over-all 5-year survival rate of 54% and a 10-year survival rate of 37%. Patients with small, well-differentiated cancer discovered by suprapubic prostatectomy need not have a secondary radical prostatectomy; estrogens or castration do not seem to alter the prognosis in this group. Secondary radical prostatectomy may be a rational approach for treating the moderately or poorly differentiated and the large cancers.

Journal of Bone and Joint Surgery, Boston

42A:193-374 (March) 1960. Partial Index

Myelograms and Findings in Lumbar Disc Lesions
W. E. Lansche and L. T. Ford ....p. 193
Congenital Dislocation of the Knee
J. J. Niebauer and D. E. King ....p. 207
Experiences with the S.A.C.H. Foot Prosthesis
E. J. Gordon and J. Ardizzone ....p. 226
Deformity Following Supracondylar Fractures of Humerus
L. Smith ....p. 235
The Versatile Cross-Finger Pedicle Flap
H. D. Hoskins ....p. 261
Osteochondritis of the Knee Joint
A. D. Smith ....p. 289
Anterior Spine Fusion for Tuberculosis of the Spine
A. R. Hodgson and F. E. Stock ....p. 295

The Myelogram and Findings in Lumbar Disk Lesions.—The authors report on 866 patients from whom myelograms were obtained. Of these patients, the cases of 660 were analyzed in detail: 447 (67.8%) were men with an average age of 41.6 years, and 213 (32.2%) were women with an average age of 41.2 years; 90.8% of the patients had low back pain with sciatica; and 5.9% had sciatica only. In 57.5% of the patients there was a history of injury of varying magnitude before the onset of symptoms. The 660 patients were operated on and 704 disks were removed. A large lateral indentation of the dye column, observed on the anteroposterior view, was usually associated with a ruptured disk and occurred in 62.9% of the defects which were noted in the myelogram. An hourglass deformity, produced by a midline herniation of the disk, occurred in 16.4% of the defects revealed by the myelogram. Asymmetry, elevation, or nonfilling of the nerve-root sleeve on one side, which may be indicative of herniation of the disk, occurred in 14.9% of the defects. Block type defects occurred in 5.8%. These positive myelographic findings were confirmed by the operative findings in 513 of the 660 patients, giving an accuracy of 77%. Major discrepancies between the myelographic and operative findings were observed in 110 patients (17%). Relatively unimportant discrepancies were present in 37 patients (6%). Six extradural and 3 intradural neoplasms, masquerading as ruptured intervertebral disk lesions, occurred among the 866 patients, representing an incidence of 1%. Even with myelograms, only 2 intradural tumors, of the total of 9 neoplasms, were diagnosed definitely before the operation. Myelography should routinely precede surgery for lumbar disk lesions.

Congenital Dislocation of the Knee.—The authors report on 3 male and 9 female patients with congenital dislocation of the knee. There were 3 boys and 8 girls between the ages of 1 day and 12 years, and 1 woman who was 67 years of age. Two patients had a family history of what seemed to be similar dislocations. Deformity of the epiphysis around the knee occurred in the older but not in the younger patients, suggesting that the deformity may be a secondary change similar to that seen in the femoral head in older patients with untreated dislocation of the hip. Six of the children and the woman had dislocations of both knees.

Of the 19 dislocations which were present in these 12 patients, 4 were treated successfully shortly after birth by manipulative reduction (flexion of the knee) and immobilization of the extremity with the knee in flexion. Six knees in which immediate manipulative reduction was not possible were treated by a preliminary period of traction which was then followed by manipulation and immobilization in plaster. An open reduction is indicated when closed methods fail. It was necessary to operate on 6 knees. Arthrodesis was the only form of treatment applicable to the knee of the 12-year-old girl with a severe long-standing deformity. The severe dislocations of both knees in the woman had not been treated, but she was able to walk quite well. Obviously she was much better off than she would have been if her knees had been arthrodesed or if open reductions had been attempted late in childhood. With the less severe deformities, excellent results are obtained by early treatment with conservative measures. The technique of open reduction, when indicated, varies according to the deformity. Arthrodesis was necessary in only 1 of the 19 knees reported on.

Anterior Spine Fusion for Spinal Tuberculosis.—The authors report on 100 consecutive patients with tuberculosis of the vertebrae (Pott's disease) who were treated surgically. Forty patients were aged up to 5 years, 29 were aged 6 to 10 years, and 31 were aged 11 to 70 years. The distribution of the disease was maximum at the 10th thoracic vertebra, the average extent of the involvement being 3 or 4 vertebrae. The spine was approached anteriorly. The abscess with its contents was removed, as were the bone sequestrums, the sequestrated intervertebral disks and all avascular bone. The spine was fused with an anterior strut graft. The patients were followed carefully after discharge from the hospital, routine roentgenograms being performed every 3 months. The follow-up period varied from 2 to 4 years. All patients were given maintenance therapy with antituberculosis drugs for from 18 months to 2 years. Four of the patients died, 1 of pulmonary edema and cardiac failure, 1 of generalized tuberculosis, 1 of hepatic failure occurring 7 days after cholecystectomy and after the patient had recovered from the spine fusion, and 1 of postoperative pneumonia 7 days after the spine fusion. Three of these deaths might have been prevented. Healing, consisting of the disappearance of the destructive lesion, a firm bony ankylosis between the remaining portions of the involved vertebrae, and the restoration of a normal consistency to the surrounding bone, was obtained in 93 patients. A 2nd operation was required in order to obtain the same good result in 1 other patient. Nonunion of the bone resulted in the remaining 2 patients, but these patients were symptom-free. Although most of the patients treated had an advanced form of the disease, involving many vertebrae, the best and most gratifying results were obtained in patients with early lesions.

Journal Laboratory & Clinical Medicine, St. Louis

55:497-662 (April) 1960. Partial Index

Respiratory Illness Due to Asian Influenza
I. Schultz and others .... p. 497
Hemagglutination Test for Viral Hepatitis
E. R. Jennings and C. Hindmarsh .... p. 519
Serum Arginase Activity in Hepatocellular Damage
G. Ugarte and others .... p. 522
Survival Time of Leukocytes in Leukemic Patients
P. K. Lala and others .... p. 548
Urine Culture in Urinary Tract Infection
S. Switzer .... p. 557

Respiratory Illness Due to Asian Influenza.—The authors studied clinical manifestations and symptoms of respiratory illnesses in 210 hospitalized Navy recruits. Asian strain influenza, which was present in 112 patients, was characterized by sudden onset, headache, malaise, sore throat, nonproductive cough, nasal symptoms, and nonlocalizing physical findings. Type 4 adenovirus infection, which was present in 64 patients, was characterized by gradual onset, sore throat, malaise, dysphagia, hoarseness, nasal symptoms, headache, and findings of pharyngeal inflammation with or without exudate. Thirty-four patients, in whom influenza, adenovirus infection and streptococcic infection had been ruled out, showed symptoms resembling influenza clinically but manifested a higher incidence of pneumonia. These illnesses appeared to have diverse etiologies. Pneumonia, which appeared to be a part of the viral infection, was diagnosed by roentgenologic examination in 10 of the patients with influenza and in 7 of those with adenovirus infections. The data of this report reemphasize the importance of clinical observations in the diagnosis of viral respiratory infections.

Journal of Pathology and Bacteriology, Edinburgh

79:1-220 (Jan.) 1960. Partial Index

Scirrhous Adenocarcinoma Arising in Lipomatous Pancreas
R. Salm .... p. 47
Detecting Acid-Fast Organisms by Fluorescence Microscopy
S. W. A. Kuper and J. R. May .... p. 59
Intermittent Complete Renal Ischaemia
H. L. Sheehan and J. C. Davis .... p. 77
Phaeochromocytoma of Urinary Bladder
R. C. B. Pugh and others .... p. 89
Fat and Oxidative Enzymes in Fatty Livers
R. L. Friede .... p. 109
Vascular Invasion in Lung Cancer
D. M. Pryce and J. B. Walter .... p. 141

Vascular Invasion in Lung Cancer.—The proximity of lung cancers to large blood vessels permits tumor tissue to invade pulmonary arteries and veins. Cases have been cited in which death was due to massive hemorrhage from an eroded pulmonary artery, and venous invasion has been thought to play a major part in embolic spread. In their studies the authors found that neoplastic invasion of veins and arteries, even when gross, is easily overlooked; but in the careful examination of 183 resected cancers of the lung they found gross vascular invasion in 61.2%, arterial 43.2%, venous 40.0%. In 21.9% of cases both arteries and veins were invaded. It was found that 31.6% of the small tumors, 66.6% of the medium, 73.2% of the large, and 57.1% of the giant tumors showed either arterial or venous invasion. Vascular invasion of veins, arteries, or both was less common in tumors of definitely, central origin than in those of definitely peripheral origin, the comparative figures being 40 and 61%. The greater tendency of peripheral tumors to vascular invasion is shown even more clearly by comparing peripheral and central tumors of comparable size and similar histological type. In 43 patients, in whom the site of origin of the tumor could not be ascertained, gross vascular invasion was more frequent (83%). Investigation of the importance of the histological type of tumor disclosed that gross vascular invasion was most frequent in the oat-cell type of tumor (74%). The authors gained the impression that embolism from gross vascular invasion is probably more important in the formation of metastases than in cellular dissemination from microscopic vessels.

Journal of Urology, Baltimore

83:211-322 (March) 1960. Partial Index

Renal Agenesis and Dysgenesis
D. J. B. Ashley and F. K. Mostofi ....p. 211
Atheromatous Embolism as Cause of Renal Failure
R. M. Greendyke and Y. Akamatsu ....p. 231
Mesenchymal Hamartomas of Kidney
M. L. Perou and P. T. Gray ....p. 240
Wilms's Tumor with Cystic Renal Disease
A. C. Uson and others ....p. 262
New Method of determining Residual Urine Volume
H. A. Hershman ....p. 283
Production of Collateral Blood Supply to Bladder
H. L. Warres ....p. 290
Recurrence of Bladder Tumors
F. Hinman Jr. ....p. 294
Acute Urinary Retention Due to Fecal Impaction
A. Grunberg ....p. 301
Perineal Punch Biopsy in Prostatic Carcinoma
M. W. Thomley and others ....p. 305

Atheromatous Embolism as Cause of Renal Failure.—The authors report the clinical and pathological findings in 3 cases in which renal failure was either clinically unexplained or was attributed to causes other than atheromatous embolism. The 1st patient gave the impression that he had an abdominal aortic aneurysm, with probable encroachment on the renal arteries, and secondary uremia. At autopsy, the right coronary artery was found to be occluded by a thrombus. A single embolus in the right lung was associated with a recent pulmonary infarct. The entire aorta exhibited arteriosclerotic changes, with many ulcerations of plaques. Atheromatous emboli, of the type found in the kidneys, were also found in the pancreas, gallbladder, colon and prostate.

In the 2nd patient, the clinical impression was that he had hypertensive cardiovascular disease, nephrosclerosis, and arteriosclerotic aneurysm of the aorta, with possible involvement of the renal arteries, and terminal rupture. Microscopic examination of the kidney showed changes similar to those observed in the 1st patient. In the 3rd patient, the cause of death appeared to be uremia, probably due to nephrosclerosis. Autopsy disclosed enlargement of the heart, with focal scarring of the left ventricular myocardium, emphysema, marked edema, and evidence of chronic passive hyperemia in the lungs. The aorta, especially in its abdominal portion, evidenced severe arteriosclerosis and erosion of numerous plaques. The kidneys showed numerous old and recent atheromatous arterial emboli. The authors suggest that atheromatous embolization of the renal arteries should be considered in the differential diagnosis of elderly patients with unexplained renal failure.

Lancet, London

1:345-396 (Feb. 13) 1960. Partial Index

Immediate Treatment of Cerebral Infarction
A. B. Carter ....p. 345
Uncomplicated Acute Tubular Necrosis
L. Loughbridge and others ....p. 351
Cryptogenic Liver Abscess
J. F. Stokes ....p. 355
Trial of Bacterial Vaccines for Common Cold
D. L. Miller and others ....p. 358
Dyspepsia due to Inhalation of Carbon Tetrachloride Vapor
G. Kazantzis and R. R. Bomford ....p. 360

Dyspepsia Due to Carbon Tetrachloride Vapor.—It is well known that exposure to high concentrations of carbon tetrachloride vapor produces narcosis and liver and kidney damage. It is not so well known that exposure to lower concentrations may be responsible for other less serious effects. The authors examined 15 of the 18 persons employed in a factory, who complained of anorexia, nausea, occasional vomiting, and abdominal discomfort not amounting to pain but associated with depression, which was the most pronounced symptom. Because the complaints were better at weekends but increased in severity in the last half of each working week, a detailed investigation of the patients' work was conducted. It was found that these factory workers were exposed to the vapor of carbon tetrachloride. Necessary precautions were taken to reduce future exposure, and all the workers were symptom-free within 1 week. There were no recurrences up to 6 months later. These findings show that a concentration of carbon tetrachloride vapor of the order of 45-100 parts per million in the working environment can be associated with the appearance of symptoms of poisoning.

Minerva Cardioangiologica, Turin

7:605-696 (Dec.) 1959. Partial Index

Drainage in Cardiac Surgery
P. Caluzzi and others ....p. 605
Panarteritis Nodosa with Diabetes Mellitus
G. Toja and G. Ambrassa ....p. 607
Cerebroretinal Circulation in Cerebrovascular Episodes
P. Trivella and G. Venturi ....p. 668

Cerebroretinal Circulation.—The authors report on the findings of opthalmometric examination according to the technique of Weigelin in 30 patients, aged 45 to 75 years, with a focal encephalopathy related to cerebrovascular disorders. The onset of an acute cerebrovascular disorder was recent in 15 patients and in the stage of stabilization in the other 15. Cerebral thrombosis was diagnosed in 26 patients, meningeal hemorrhage in 2, and probable thrombosis of the internal carotid artery in 2. Arterial pressure of the retina was higher than arterial pressure of the humeral artery in patients with cerebral hemorrhage. Of 2 patients with meningeal hemorrhage, arterial pressure of the retina was higher than pressure of the humeral artery in one and lower in the other. There was a discordance of the retinal pressure values of the eyes in both patients with thrombosis of the internal carotid artery, and hypotension was observed on the side of the cerebral lesion. The retinocerebral circulation appeared almost identical in patients with a cerebral lesion of either recent or remote onset.

The authors believe that opthalmometric examination according to the technique of Weigelin is a convenient procedure for diagnosis and prognosis of acute cerebrovascular episodes. This method is particularly useful in instances where arteriography is not feasible.

Minerva Medica, Turin

51:1-56 (Jan. 6) 1960. Partial Index

Study of Dysproteinemia in Silicosis
W. Paolino and others ....p. 1
Cardiovascular and Pulmonary Involvement in Asbestosis
G. Scansetti and G. F. Rubino ....p. 8
Intoxication by Benzene: Radioisotopes Used as Tracers
W. Paolino and L. Resegotti ....p. 33

Intoxication by Benzene.—A suspension of benzene in olive oil was injected intramuscularly into each of 18 rabbits for the purpose of studying the pathogenic mechanism of anemia in relation to benzene intoxication. The dosage used was 4 doses of 1 cc. (400 mg.) each per kilogram of body weight every other day. Another 3 animals were kept as control group. Fe^{59} and Cr^{51} were used as tracers. Decrease in the erythrocyte count took place after 2 injections and became marked after 4. Simultaneously the animals lost weight and appetite, and they developed diarrhea and paralysis of the posterior limbs. There was a gradual increase of the clearance rate of iron in the plasma after the 2nd injection. It increased again after the 4th injection, and it became even more marked 7 days after the last injection.

The absorption rate of the radioiron in the hemin erythrocytes was markedly increased at the height of the intoxication period and during recovery. Blood cell count and bone marrow values confirmed this finding. The life span of the red blood cells produced during the intoxication period was shorter than normal in experiments using either Fe^{59} or Cr^{51} as erythrocyte tagging agents. The progression rate of anemia was higher than expected. This fact cannot be explained on the basis of the findings of this study.

New England Journal of Medicine, Boston

262:585-636 (March 24) 1960. Partial Index

Anaphylactoid Reactions to Oral Penicillin
J. M. Batson ....p. 590
Blood in Citrate Phosphate Dextrose During Surgery
J. G. Gibson and others ....p. 595
Declining Severity of Rheumatic Fever
E. F. Bland ....p. 597

Anaphylactoid Reactions to Oral Penicillin.—Anaphylactoid reactions are known to occur after parenteral administration of penicillin but they are extremely rare after oral administration. When 1 patient with such a reaction was observed at the New York Hospital, the records of this hospital were reviewed and an additional unreported case was found. Both patients recovered. Data on these 2 patients, and on 26 others collected from English medical literature, are given. The symptoms in all began less than one-half hour after ingestion of penicillin. The most common symptom was unconsciousness, which was present in 22 of the 28 cases. Gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and an urge to defecate occurred in 12 patients; skin reaction in 10; facial edema, cyanosis, respiratory distress, or all 3, in 8; facial numbness or pruritus, or both, in 6; convulsions in 3; and severe chest pain in 2. Other symptoms included dizziness, weakness, "bad taste," anxiety, and headache. The duration of the symptoms before therapy varied from a few minutes to 2 hours. The treatment varied greatly; adrenergic agents, antihistamines, and oxygen were used most commonly. Five patients recovered without therapy. Two of the 28 patients died from the reaction. Of the 26 who survived, 6 later had other severe reactions to penicillin. Although the oral route seems to be safer than the parenteral, its use is not without dangers.

Declining Severity of Rheumatic Fever.—This report is based on the long-term studies of rheumatic fever at the House of the Good Samaritan from 1921 onward. About 3,500 children and adolescents with rheumatic fever have been admitted to this institution at the rate of 100 new cases per year. Only patients whose illness on admission represented the initial attack have been considered. The first 100 consecutive cases in each of the 4 succeeding decades have been compared. In terms of severity the most significant features of rheumatic fever are the incidence and degree of carditis at time of onset, as indicated by enlargement of the heart, by murmurs, and by the mortality in the 1st year of the disease and in the ensuing 5 years. Tabulated data indicate a gradual and progressive change for the better. The most striking features have been: a modest decline in the incidence of cardiac involvement in terms of residual murmurs (from 75% in 1921-1922 to 60% in 1950-1951); a twofold amelioration in the degree of carditis as indicated by heart size; and an eightfold reduction in mortality. Among factors that contributed to the change, improvement in standards of living among the poorer classes in urban areas is perhaps of 1st importance. General measures aimed at the protection of patients and the isolation of carriers may have been of help even before more specific therapy was available. Nevertheless, it was at this time that sulfonamide compounds were introduced and prophylactic programs instituted. One cannot discount a natural mutation of the disease as a result of a new generation of more resistant hosts and less vigorous organisms. A decline in the severity of rheumatic fever was well under way even before the advent of penicillin and other antibiotics.

North Carolina Medical Journal, Winston-Salem

21:45-88 (Feb.) 1960. Partial Index

Salmonella Osteomyelitis with Sickle Cell Anemia
W. A. Dunnagan ....p. 45
Nonhormonal Adrenal Carcinoma
A. Freedman and others ....p. 55
Silo-Filler's Disease: Report of 2 Cases
E. G. Evans Jr., L. B. McDonald, and R. A. Porter ....p. 59
The Role of the Physician in a Changing Society
H. A. Matthews ....p. 65

Silo-Filler's Disease: Report of Two Cases.—The authors present the clinical histories of 2 patients which, they believe, conform to the established criteria for particular forms of silo-filler's disease. Both cases involved exposure to fresh silage: the 1st to corn silage, 2nd to silage of the legumes, alfalfa, and clover, together with some pasture grasses. It has been demonstrated that silo-filler's disease involves exposure to gas evolved from fresh silages during the initial fermentation stages of ensiling. This irritating gas has been identified as nitrogen dioxide and its dimer, nitrogen tetroxide. It has been suggested by Lowry and Schuman that there is a continuous spectrum of different types and degrees of bronchopulmonary injury by nitrogen dioxide (dependent chiefly upon the amount of gas inhaled), from the rapidly fatal acute pulmonary edema, or bronchopneumonia, to bronchiolitis fibrosa obliterans, which may cause death after several weeks; and from bronchiolitis and focal pneumonitis with spontaneous recovery to chronic pulmonary fibrosis and emphysema. Case 1, in the present report, appears to correlate closely with the criteria for silage gas-induced bronchiolitis fibrosa obliterans. Case 2 appears to fall within the bronchiolitis and focal pneumonitis category. The authors stress that both of the patients responded favorably to corticosteroid therapy and that there is need for the dissemination of more concrete information about the potential dangers to persons engaged in ensiling.

Ugeskrift for laeger, Copenhagen

122:239-270 (Feb. 25) 1960. Partial Index

Treatment of Ischialgia: Bed-Rest or Mobilization
E. S. Staffeldt ....p. 239
Progesterones: Use in Hepatic Cirrhosis
P. Hempel-Jorgensen and P. Eilersen ....p. 244

Treatment of Ischialgia: Bed Rest or Mobilization.—Active treatment combined with early mobilization was applied in 100 patients with the ischialgia syndrome, and another 100 patients with the syndrome were treated with long-continued strict confinement to bed. Active treatment resulted in an essentially shorter course, measured by duration of pain, Lasègue's sign, and duration of hospitalization. Hospital stay averaged 30 days for the 1st group and 50 days for the 2nd group. No aggravation of symptoms or objective changes indicated that active treatment caused prolapse or increased the prolapsing already manifest. Prolonged confinement to bed should be abandoned for patients with the ischialgia syndrome in favor of exercise therapy and early mobilization.

WASHINGTON NEWS

Health Bill Held Up . .
Labelling Plan Through Congress . .
A. M. A. Stand on Health Measure . .
Administration Stand . .
Miscellany . .

FINAL CONGRESSIONAL ACTION ON HEALTH BILL PUT OFF UNTIL AFTER POLITICAL CONVENTIONS

The House-approved health bill for the elderly was taken up at two days of open hearings by the Senate Finance Committee, but final congressional outcome of the legislation was postponed until after the Democratic and Republican conventions.

The measure was one of three or four major legislative items still left on the docket as the Fourth of July weekend approached and Senate Majority Leader Lyndon B. Johnson (D., Tex.) and House Speaker Sam Rayburn (D., Tex.) decided to call a one-month recess.

The unusual summer break of Congress meant that the health care for the aged issue will not be resolved in Congress until sometime in August. What effect the delay would have on the legislation was conjectural.

The voluntary, federal-state plan to assist the elderly who need help in meeting health bills was overwhelmingly approved by the House, 381 to 23. But Senate backers of compulsory plans under Social Security promised every effort to try and substitute a government medicine plan under the Social Security system.

If the Senate should approve a different bill from the one cleared by the House, it would be necessary for a House-Senate conference committee to try and resolve differences in the two measures.

LABELLING BILL TO WHITE HOUSE

The Senate passed and sent to the White House a bill requiring precautionary labelling of household substances containing poisonous or hazardous materials.

The bill, strongly backed by the American Medical Association, covers poisonous, corrosive, flammable, and other types of chemicals not regulated by existing laws, as well as some radioactive substances contained in silver polishes, dry cleaning preparations, and similar cleansers.

An estimated 600,000 children swallow household substances every year, and about 500 die annually. Many adults also are killed and injured from this cause.

The bill was drawn up after conferences with interested industry groups, physicians, and lawyers. It calls for instructions on how to use the materials and first-aid advice in case of injury, as well as words like "danger" and "keep out of the reach of children."

Packages not labelled properly would be subject to seizure and violations subject to a $200 fine, 90 days in jail, or both. Congress did not include in the bill A. M. A.-endorsed provisions to cover all hazardous substances, not just those employed in household use, and for pictorial warning symbols such as a flame or skull and crossbones.

A. M. A. ENDORSES HOUSE HEALTH BILL

The American Medical Association urged the Senate to pass a House-approved bill to provide health care for the aged under a voluntary, federal-state, program.

Dr. Leonard W. Larson of Bismarck, N. D., President-elect of the A. M. A., presented the Association's stand to the Senate Finance Committee which held two days of hearings on the bill before the Convention recess.

This legislation "merits the support of everyone familiar with the problem," Dr. Larson said.

The A. M. A. spokesman said the legislation should be supported on three counts:

1. It is designed to help those who really need help. "It does not make the mistake of treating all of our 15.5 million older people as hardship cases. It aids those who need aid, and thereby preserves the right of the non-needy to take care of themselves."

2. By limiting its effect to the near-needy minority, the bill "allows the majority to continue its use of the voluntary method—private health insurance and pre-payment plans. This measure is in no sense compulsory."

3. The individual states are made "primarily responsible" for the administration of the plan—not the federal government." This is as it should be. We are convinced that the health care costs of the needy and non-needy can best be determined locally, and cannot either be determined or met through mechanisms operating out of Washington, D. C."

Dr. Larson said: "Regrettably, the financing of medical care for the aged has produced violent controversy both in and out of Congress. There seems to be two schools of thought on how this should be handled.

"On the one hand are the proponents of OASDI (Social Security) health care amendments, who propose that a radical change be made in what is essentially a cash benefit program. Disregarding the fact that such a course can lead only to State medicine, the advocates of this approach call for federal intervention via compulsory Social Security taxation for the financing of medical benefits for all OASDI beneficiaries—regardless of need.

(Continued on next page)

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 1.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-30.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 26-29.
1963 Annual Meeting, Atlantic City

AMERICAN

1960

July

American Society of Facial Plastic Surgery, Hotel Elysee, New York City, July 22. Dr. Samuel M. Bloom, 123 E. 83d St., New York 28, *Secretary.*

Flying Physicians Association Hawaii Cruise, leaving *Los Angeles* and San Francisco. July 11. For information *write: Mr. Mark E. DeGroff,* P. O. Box 3275, Tulsa, Okla.

Postgraduate Medical Assembly of South Texas, The Shamrock Hilton, July 18-20. Mrs. W. H. Dahme, 412 Jesse H. Jones Library Bldg., Texas Medical Center, Houston 25, Executive Secretary.

Rocky Mountain Cancer Conference, Hilton Hotel, Denver, July 20-21. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary, Colorado State Medical *Society.*

August

American Association of *Blood* Banks, *Jack Tar* Hotel, San Francisco, Aug. 21-26. For information write: AABB Central Office, Suite 1619, 30 N. Michigan, Chicago 2.

American Congress of Physical Medicine and Rehabilitation, Mayflower Hotel, Washington, D. C., Aug. 21-26. Mrs. *Dorothea C.* Augustin, 30 N. *Michigan* Ave, Chicago 2, Executive Secretary.

American Hospital Association, Civic Auditorium, San Francisco, Aug. 27-Sept. 1. Mr. Maurice J. Norby, 840 N. Lake Shore Dr., Chicago 11, Secretary.

American Institute of Ultrasonics in Medicine, Statler-Hilton Hotel, Washington, D. C., Aug. 20. Dr. Dorothy M. Stillwell, *Dept. of Phys.* Med. and Rehab., Univ. of Colorado Med. Center, Denver 20, Chairman.

American Physiological Society, *Stanford University*, Calif., Aug. 22-26. Mr. Ray G. Daggs, 9650 *Wisconsin* Ave., *Washington* 14, D. C., Executive Secretary.

American Society of Clinical Hypnosis, Miami, Fla., Aug. 7-10. Dr. *Seymour Hershman*, 6770 N. Lincoln Ave., Chicago 46, Secretary.

American Society for Pharmacology and Experimental Therapeutics, University of Washington, *Seattle*, Aug. 21-25. Dr. Karl H. Beyer, Merck Sharp & Dohme Research Laboratories, West Point, Pa., Secretary.

American Veterinary Medical Association, Denver-*Hilton* Hotel, Denver, Aug. 15-18. *H. E. Kingman Jr.*, 600 S. Michigan Avenue, Chicago 5, Executive Secretary.

Biological Photographic Association, Inc., Utah Motor Lodge, Salt Lake City, Utah, Aug. 23-26. *Miss Jane H.* Waters, Box 1668, Grand Central P. O., New York 17, Executive Secretary.

Conference on the Chemical Organization of Cells: Normal and Abnormal, *University of* Wisconsin, Madison, Aug. 25-27. Dr. J. F. A. McManus, Dept. of *Pathology*, University of Alabama *Medical Center,* Birmingham, Chairman.

Gerontological Society, Inc., Mark Hopkins Hotel, San Francisco, Aug. 7-12. Mrs. Marjorie Adler, 660 S. Kingshighway Blvd., St. Louis 10, *Administrative Secretary.*

National Medical Association, Inc., Penn-Sheraton *Hotel*, Pittsburgh, Aug. 8-11. Dr. John T. Givens, 1108 Church St., Norfolk, Va., Executive *Secretary.*

Reno *Surgical* Society, Mapes *Hotel*, *Reno*, *Nev*, Aug. 18-20. Dr. Gilbert G. Lenz, 505 S. Arlington Ave., Reno, *Nevada.*

Rocky Mountain Radiological Society, Denver-Hilton Hotel, Denver, Aug. 11-13. Dr. John H. Freed, 4200 E. 9th Ave., Denver 20, Secretary-Treasurer.

St. Joseph's Hospital Annual Clinics, St. Joseph's Hospital, Denver, Aug. 3-5. Dr. W. H. Leitch, St. Joseph's Hospital, 1818 Humboldt St., Denver 18, Chairman.

West Virginia *State* Medical Association, The Greenbrier, White *Sulphur Springs*, Aug. 25-27. Mr. Charles Lively, Box 1031, Charleston 24, W. Va., Executive Secretary.

September

American Academy of Pediatrics, and American Academy of General Practice, *Louisiana Chapter*, Roosevelt *Hotel*, New Orleans, Sept. 23. Dr. Herbert B. Rothschild, 1520 Louisiana Ave., New Orleans 15, Chairman of Publicity Committee.

American Medical Writers' Association, Hotel Morrison, Chicago, Sept. 30-Oct. 1. *Dr. Harold Swanberg*, 510 Maine St., Quincy, Ill., Secretary.

American Roentgen Ray Society, Ambassador Hotel, Atlantic City, Sept. 27-30. Mr. Hugh Jones, 20 N. Wacker Dr., *Chicago 6, Director, Public Relations.*

American Society of *Clinical Pathologists*, Palmer House, Chicago, *Sept.* 24-Oct. 2. Mr. Claude E. Wells, 445 Lake *Shore* Drive, Chicago 11, Executive Secretary.

College of American Pathologists, Palmer House, *Chicago, Sept.* 24-27. Dr. Arthur H. Dearing, 2115 *Prudential* Plaza, Chicago, Executive Director.

Colorado State Medical Society, Stanley Hotel, Estes Park, Sept. 14-17. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary.

Delaware, Medical Society of, Rehoboth, Del., Sept. Mr. Lawr C. Morris Jr., 1925 Lovering Ave., *Wilmington* 6, Del., Execu Secretary.

Flying Physicians *Association*, third clinical meeting, Western Lodge, Wagoner, *Okla.*, Sept. 6-9. For information write: Flying Ph cians Association National Headquarters, P. O. Box 3275, Tulsa, O

Inter-Society Cytology Council, Palmer House, Chicago, Sept. 2 Dr. Paul A. Younge, 1101 Beacon St., Brookline 46, Mass., Secret

Kentucky State Medical Association, Louisville, Sept. 20-22. J. P. *Sanford*, 1169 Eastern Parkway, Louisville 17, Ky., Execu *Secretary.*

Maryland, Medical and Chirurgical *Faculty of the State* Semiannual Meeting, Ocean City, Sept. 16. Mr. *John Sargeant,* Cathedral St., Baltimore 1, Executive Secretary.

Michigan State Medical Society, Detroit, week of Sept. 25. Dr. Bruce Wiley, 606 Townsend St., Lansing 15, Mich., Secretary.

Montana Medical Association, Baxter Hotel, Bozeman, Sept. 15-17. Dr. William E. Harris, 114 N. Second, Livingston, Montana, Secretary.

National Cancer *Conference*, *American* Cancer Society, Inc., and the National Cancer Institute, Minneapolis, Minnesota, Sept. 1 15. Dr. Roald M. Grant, 521 W. 57th St., New York 19, Coordinator.

National Recreation Congress, Shoreham Hotel, Washington, D. C., Sept. 25-29. Willard B. Stone, 8 W. Eighth St., New York 11, Secretary.

Nevada State Medical *Association*, Stardust Hotel, *Las Vegas*, Sept. *7-10. Mr. Nelson B. Neff,* P. O. Box 2790, Reno, Nev., Executive Secretary.

New England Society of *Anesthesiologists*, Bretton Woods, N. H., Sept. 18-19. Dr. Thomas K. Burnap, P. O. Box 81, Kenmore Station P. O., Boston 15.

Oregon State Medical *Society*, *Portland*, Sept. 7-9. Mr. Roscoe K. Miller, 2164 *S.* W. Park Place, *Portland* 5, Ore., Executive Secretary.

Pacific Dermatologic Association, Empress Hotel, Victoria, British Columbia, Canada, Sept. 1-4. Dr. Edward J. Ringrose, 2636 Telegraph Ave., *Berkeley* 4, *Calif.*, Secretary-Treasurer.

Society for Pediatric Radiology, Ambassador Hotel, Atlantic City, N. J., *Sept.* 26. Dr. Richard G. Lester, 412 Union St., S. E., Minneapolis 14, Minn,, Secretary-Treasurer.

Southern Trudeau *Society* (and Southern Tuberculosis Conference), Hotel Francis Marion, Charleston, S. C., Sept. 14-16. Mr. Judson M. Allred Jr., P. O. Box 9865, Northside Station, Jackson, Miss., Secretary-Treasurer.

Tennessee Valley Medical Assembly, Read House, Chattanooga, Tenn., Sept. 26-27. Dr. Robert A. Waters, 109 Medical Arts Bldg., Chattanooga, Chairman.

Tri-State Medical *Assembly*, *Captain* Shreve Hotel, Shreveport, La. Sept. 14-15. Dr. J. W. Wilson Jr., 940 Margaret Place, Shreveport, La, Secretary-Treasurer.

Utah State Medical Association, Hotel Utah Motor Lodge, Salt Lake City, *Sept.* 20-23. Mr. Harold Bowman, 42 S. 5th *East*, *Salt Lake City* 2, *Executive Secretary.*

Washington State Medical Association, Seattle, Sept. 25-28. Mr. Ralph W. Neill, 1309 Seventh Ave., *Seattle* 1, Executive Secretary.

Wyoming State Medical Society, Jackson Lake Lodge, Moran, Sept. 7-10. Mr. Arthur R. Abbey, P. O. Box 2036, Cheyenne, Wyo., Executive Secretary.

October

Academy of Psychosomatic Medicine, Benjamin Franklin Hotel, Philadelphia, Oct. 13-15. For information write Dr. *Bertram B. Moss*, 55 E. Washington, Chicago 2.

American Academy for Cerebral Palsy, Penn-Sheraton Hotel, Pittsburgh, Oct. 5-8. Dr. Joseph D. Russ, 1520 Louisiana Ave., New Orleans 15, *Executive* Secretary.

American Academy of *Ophthalmology & Otolaryngology*, Palmer House, Chicago, Oct. 9-14. Dr. William L. Benedict, 15 Second St. S. W., Rochester, Minn., Executive Secretary.

American Academy of Pediatrics, Palmer House, Chicago, Oct. 17-20 Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.

American Association of Medical *Clinics*, *New Orleans*, *Oct.* 6-8. Dr. Joseph B. Davis, 134 N. Washington St., Marion, Ind., Secretary.

American Association of Medical Record Librarians, Olympia Hotel Seattle, Oct. 10-13. Miss Doris Gleason, 840 N. Lake Shore *Dr.*, Chicago 11, Executive *Director.*

American Association of *Poison* Control Centers, Palmer House Chicago, Oct. 18. Dr. Harry C. Shirkey, 712 S. 30th St., Birmingham, Ala., Chairman, Program Committee.

American *Association* for the Surgery of Trauma, Coronado Hotel Coronado, Calif., Oct. 5-7. Dr. William T. Fitts Jr., 3400 Spruce St. Philadelphia 4, Secretary.

American College of Gastroenterology, *Bellevue-Stratford* Hotel, *Philadelphia*, Oct. 23-26. Mr. Daniel Weiss, 33 W. 60th St., New York 23, Executive Director.

American College of Surgeons, Clinical Congress, San Francisco, Oct. 10-14. For information write: *Dr. William* E. Adams, 40 E. Erie *St., Chicago* 11.

American Fracture Association, El Presidentia *Hotel*, *Mexico*, *D. F.*, Mexico, Oct. 30-Nov. 4. Dr. H. W. Wellmerling, *610 Griesheim* Bldg., Bloomington, Ill., Executive *Secretary.*

American Heart Association, Inc., Jefferson Hotel, St. Louis, Oct. 21-25. Mr. Rome A. Betts, 44 E. 23rd St., New York 10, Executive Director.

American Otorhinologic Society for *Plastic Surgery*, Inc., Conrad Hilton, Chicago, Oct. 9. Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, L. I., New York, *Secretary.*

American Public Health Association, San Francisco, Oct. 30-Nov. 4. Dr. Berwyn F. Mattison, 1790 Broadway, *New York* 19, Executive Director.

American *Rhinologic* Society, Belmont Hotel, Chicago, *Oct.* 8. Dr. Robert M. Hansen, 1735 *N.* Wheeler Ave., Portland 17, *Ore.*, Secretary.

American School Health Association, *San Francisco*, Oct. 30-Nov. 4. Dr. A. O. DeWeese, 515 E. *Main St.*, Kent, Ohio, Executive Secretary.

American *Society* of Anesthesiologists, Inc., Statler-Hilton, New York City, *Oct.* 2-7. Mr. John W. Andes, 515 Busse *Hwy.*, Park Ridge, Ill., Executive Secretary.

(Continued on page 38)

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ADDRESS TO THE HOUSE OF DELEGATES

E. Vincent Askey, M.D., Los Angeles

TODAY I should like to call your attention to a few specific areas which I believe demand careful study and concerted effort by the entire profession.

First, however, I want to pay sincere personal tribute to my predecessor, Dr. Louis M. Orr. During the past year he has carried out his presidential duties with great energy and dedication. He has been a forceful, articulate spokesman for American medicine, recognized not only by his colleagues but by the public as a whole. I hope that I can come reasonably close to the quality of leadership provided by Dr. Orr.

As we now look at the year and the decade ahead, I strongly urge intensified, accelerated effort in five particular fields: (1) medical education, (2) preparations for the White House Conference on Aging, (3) voluntary health insurance and the related problem of third party relationships, (4) membership, and (5) mental health.

Medical Education

I want to emphasize the need for constructive planning to meet the future needs of the United States in medical manpower. Although opinions and statistical estimates vary widely on the exact requirements, there is general agreement that we must bring about a steady increase in the annual number of medical school graduates during the times ahead.

Our population is increasing rapidly. The dimensions of medical knowledge are constantly changing. Medical services are becoming more and more complex. And, perhaps most important, the American people are showing greater and greater interest in health and medical needs.

Cognizant of all these factors, this House of Delegates in December, 1958, adopted a clear policy statement urging existing medical schools to consider the possibility of expanding their facilities and enrollments. It also encouraged the creation of new four-year medical schools and also two-year basic science programs by universities which can provide the proper academic and clinical setting. This expansion, it added, should be based on careful, continuing study of changing needs in medical services.

One year ago in Atlantic City—recognizing the recruitment problems which already exist and which will increase with future expansions in medical education—you, the delegates, asked the Board of Trustees to consider the possibility of establishing a program of medical scholarships to be sponsored wholly or in part by the American Medical Association.

Meanwhile, during the past year, the A. M. A., in cooperation with the Association of American Medical Colleges, has developed a program for the recruitment of qualified, dedicated young people into the study of medicine. To further this program, we have produced a kit of comprehensive materials, including a handbook, pamphlets, and speeches, in addition to exhibits and a new motion picture. Six months ago, at the Dallas meeting, this House urged medical societies and individual physicians to implement the recruitment program.

At the same time, following up on the action of last June, you also approved the creation of a special study committee to "present a scholarship program, its development, administration and the role of the American Medical Association in fulfilling it." The committee also was directed to investigate seven other major questions related to the expansion, establishment, staffing, and financing of medical schools.

President of the American Medical Association, 1960-1961. Read before the House of Delegates, 109th Annual Meeting, June 13-17, Miami Beach, Fla.

The special study committee was appointed in January, began its staff work in February, and held its first meeting early in March. In accordance with your instructions in Dallas, the committee will present its initial progress report at this meeting.

With respect to this whole picture in medical education—expansion, recruitment, scholarships, and loan funds—I should like to make the following suggestions.

1. Medical societies, medical schools, and individual physicians should make the fullest possible use of the recruitment materials now available from the A. M. A. They also should make the availability of these materials known to vocational guidance counsellors, voluntary health agencies, community and civic groups, and all other potentially interested organizations.

2. The entire profession—through information, ideas and suggestions—should give full, enthusiastic cooperation to all aspects of the special study committee's work, which has only just begun.

3. State and county medical societies should establish the closest possible liaison with the medical schools located in their own states or communities. Only through solid, mutual understanding can medical educators and practicing physicians provide the sound leadership required in this problem of expansion. Some medical educators are active, interested participants in the affairs of the medical profession. Unfortunately, however, too many medical teachers have a serious lack of knowledge concerning the objectives, motivations, and accomplishments of the A. M. A. In my opinion, one of our top priorities should go to the task of educating the educators and bringing about closer rapport between actively practicing physicians and medical faculties.

4. On all levels—national, state, and local—let us tell our positive story to service organizations, civic groups, and the general public. In short, let us bury, once and for all, the false old fable that the A. M. A. tries in any way to restrict the supply of physicians.

White House Conference on Aging

On the subject of aging and health care for the aged, I do not intend to discuss the Forand Bill, the Flemming proposal, or the generally confused legislative situation concerning medical care in Washington. Nor do I intend to report on the A. M. A.'s over-all activities in the field of aging during the past year. You already have received ample information on those aspects of the subject.

Rather, I want to focus your attention on one particular phase of this issue. It calls for a lot of hard work and greatly intensified effort during the next six months, especially on the state and local level. I refer to preparations for the White House Conference on Aging, to be held next January.

You will recall that the A. M. A. strongly supported the legislation passed by the 85th Congress, providing for the national meeting and state conferences to precede it. We stated then, and we still maintain, that it is necessary to learn the facts and the nature of a problem in order to arrive at sound, intelligent solutions. A balanced perspective in the field of aging will reveal the fallacies underlying some of the hit-or-miss legislative proposals aimed in the general direction of health care for the aged.

Since 1958, much of the A. M. A.'s activity in this field has been designed to stimulate effective participation by medicine in state and local activities related to the 1961 White House Conference on Aging. Through regional conferences, special meetings, liaison efforts, and various other mechanisms, we have been striving for two major objectives: (1) to stimulate a public climate of opinion conducive to support of medicine's position in the field of aging and (2) to alert, inform, and stimulate state medical associations to action regarding the White House Conference.

In pursuit of these objectives, in late April, 1960, the A. M. A. held a National Conference on Medicine's Participation in the White House Conference on Aging. This meeting was attended by 100 persons, including representatives of 46 constituent medical societies. It provided information and thorough discussion of the various developments and problems related to preconference activities now under way on the state and local level. I urge you to see that you make full use of all facts, reports and suggestions emanating from that April meeting in Chicago.

Some of the state conferences, preliminary to the White House Conference, already have been held. Others will be taking place at various times between now and January. It is imperative that medicine take an active, articulate part in these state conferences and other planning activities prior to the national meeting.

According to my latest information, the medical profession in at least 16 states is in a favorable position to contribute to the state's report and to provide the necessary leadership among those states' delegations to the White House Conference. However, in too many other states there is the possibility that a report unfavorable to medicine's position will be presented in January by these State Delegations. Therefore, I strongly urge you and your state societies to do everything possible to make medicine's opinions known and represented.

Health Insurance and Third Parties

With respect to health insurance, the A. M. A.'s goal is to accelerate the growth and improvement of voluntary coverage for all Americans of all ages. As a significant new step in that direction, the A. M. A. last month sponsored its first National Congress on Prepaid Health Insurance in Chicago. It was attended by 200 representatives of more than 30 national organizations involved in prepayment and insurance programs. The purpose of this highly successful meeting was to see where we now stand, what we have to do in the future, and how we might go about doing it.

The A. M. A. has been widely commended for this demonstration of leadership in the field of voluntary health insurance. For example, the New York Times—which is not always in complete agreement with medicine's viewpoints—said, in a recent editorial, "The American Medical Association deserves credit for its statesmanship in staging its conference in Chicago on health insurance plans . . . at Chicago a supreme and successful effort was made to get all those involved in health insurance on an even keel, with mutual understanding as to the course to steer by."

We hope that this May conference has laid a foundation for even greater progress in the prepayment field than has been made during the past decade. I personally urge you to act favorably and enthusiastically on any recommendations which may come before you concerning the development of a future program for national and regional conferences on health insurance.

Closely related to the subject of health insurance is the whole question of medicine's relationships with the so-called third parties involved in medical economics. In accordance with your action last June on the recommendations of the Commission on Medical Care Plans, the Council on Medical Service is working to perfect a set of guides for the medical profession in dealing with third parties. It is my understanding that these guides will be presented for your approval at the clinical meeting in December.

Meanwhile, I urge every state and county medical society to review once again the recommendations of the Commission on Medical Care Plans, as adopted and revised at the Atlantic City and Dallas meetings. Many of those recommendations suggested constructive activities to improve liaison and understanding on the state and local level. I urge that they be implemented now with all possible speed and vigor. Any third party which is trying to do a medically sound job in the field of health care should be numbered among our friends and allies.

Membership

In connection with A. M. A. membership, I want to stress two points in very brief fashion.

First, I think there is definite need for improving the A. M. A.'s relations and communications with its members. Much work has been done along these lines in recent years, but I feel that we should expand and strengthen it. While it is necessary to establish a favorable image of the A. M. A. in the minds of the general public, it is equally important to establish an even stronger image in the minds of our own members.

Second, although A. M. A. membership has been increasing steadily every year, we should direct closer attention to the thousands of physicians who are not now members of the A. M. A. In some states the numbers of such physicians seem to be disproportionate. I urge all state and county societies to study their membership requirements. Their objective, I think, should be to eliminate any eligibility rules which may prevent otherwise qualified physicians from joining county and state societies and the American Medical Association.

Mental Health

Concerning mental illness and health, I must urge upon you the great need we have in our country as a whole, and in our profession particularly, to make greater efforts toward alleviation of the apparently ever-growing problem of mental illness. Possibly the ratio of such patients is not increasing, but certainly our increasing awareness of the great numbers of persons so affected makes the problem of their proper care and treatment more urgent each year. But about mental illness, we as doctors know a great deal, and, although I am sorry to have to say this, I feel certain that we are not applying our present effective knowledge to the extent we could. We recognize that there is always some lag between growth of new knowledge and its application. But I believe that in the field of mental illness this lag is now greater than in any other medical field.

The Council on Mental Health, which was first formed in 1952, has been making great strides toward the reintegration of psychiatry within the whole framework of medicine. The basic knowledge and principles of psychiatry must be emphasized throughout medicine as working tools that all doctors need to know about and to utilize in practice. This should, and must, be our continuing goal.

Further, I would like to bring to your attention the fact that the three and one-half year study of mental illness and health in the United States which was undertaken by the Joint Commission on Mental Illness and Health has now been completed. The Joint Commission's report will appear in 10 monographs and a final summary report, all due to be published this year. The monographs cover problems of economics, manpower, available community resources, epidemiology, problems of mental illness in schools, religion and mental health, and a complete resurvey of mental hospital practices.

Finally, in this same field, but in a much larger and broader sense—indeed, in a world sense—I believe that, as doctors, we all have a greater responsibility, not to people as patients, but to people as people.

It is in this larger world sense then, during my forthcoming year as President of our Association, that I would like to dedicate myself and my work toward finding solutions to this problem, which is seemingly becoming a recognized threat to our health, to our happiness, and to our civilization. I sincerely hope you, too, will recognize this challenge and dedicate yourselves and your county and state medical societies to the task of meeting it.

CLOSED-CHEST CARDIAC MASSAGE

W. B. Kouwenhoven, Dr. Ing., James R. Jude, M.D.
and
G. Guy Knickerbocker, M.S.E., Baltimore

Cardiac resuscitation after cardiac arrest or ventricular fibrillation has been limited by the need for open thoracotomy and direct cardiac massage. As a result of exhaustive animal experimentation a method of external transthoracic cardiac massage has been developed. Immediate resuscitative measures can now be initiated to give not only mouth-to-nose artificial respiration but also adequate cardiac massage without thoracotomy. The use of this technique on 20 patients has given an over-all permanent survival rate of 70%. Anyone, anywhere, can now initiate cardiac resuscitative procedures. All that is needed are two hands.

When cardiac arrest occurs, either as standstill or as ventricular fibrillation, the circulation must be restored promptly; otherwise anoxia will result in irreversible damage. There are two techniques that may be used to meet the emergency: one is to open the chest and massage the heart directly and the other is to accomplish the same end by a new method of closed-chest cardiac massage. The latter method is described in this communication. The closed-chest alternating current defibrillator [1] that was developed in our laboratories has proved to be an effective and reliable means of arresting ventricular fibrillation. Its counter-shock must be sent through the chest promptly, or else cardiac anoxia will have developed to such a degree that the heart will no longer be able to resume forceable contractions without assistance. Our experience has indicated that external defibrillation is not likely to be followed by the return of spontaneous heart action, unless the counter-shock is applied within less than three minutes after the onset of ventricular fibrillation.

A study was undertaken of means of extending this time limitation without opening the chest. A method was sought that would provide adequate circulation to maintain the tone of the heart and the nourishment of the central nervous system. This method was to be at once readily applicable, safe to use, and requiring a minimum of gadgets.

One of the first attempts at enhancing circulation in the arrested heart was a closed-chest method reported by Boehm [2] in 1878. Working with cats, he grasped the chest in his hands at the area of greatest expansion and applied rhythmic pressure. His results were quite striking in some series of tests. Tournade and co-workers [3] reported that by an abrupt compression of the thorax of a dog in cardiac arrest blood pressures of 60 to 100 mm. Hg could be produced. No survival studies were given. Killick and Eve [4] reported that the rocking technique of artificial respiration, by which a patient is tilted about 60 degrees in each direction from the horizontal plane, will produce a change in the blood pressure at the atrium from 38 to 76 mm. Hg. Eve [5] hypothesized that this change will produce sufficient blood flow to nourish the heart and the brain. In 1947 Gurvich and Yuniev [6] found that a capacitor discharge sent through the chest of a dog would be followed by a resumption of the cardiac function if applied not later than one or one and one-half minutes after the onset of induced ventricular fibrillation. They reported that this time limitation might be extended to as long as eight minutes by rhythmical application of pressure on the thorax in the region of the heart. In tests which lasted 10 to 15 minutes 19 animals survived and 17 died. These authors, however, gave no specific information as to the method of application of the pressure. Rainer and Bullough [7] treated cardiac arrest in children by lowering the head about 10 degrees, placing one arm underneath the patient's knees, and flexing the legs and buttocks against the chest. They reported eight successful resuscitations in patients ranging from 8 weeks to 13 years in age. Stout [8] in 1957 reported the successful use of this method in one adult.

Experiment

With dogs used as the experimental animal, cardiac arrest in the form of ventricular fibrillation was induced. In the initial experiments more than 100 dogs, weighing from 5 to 24 kg. (11 to 52 lb.), were used in testing various methods of moving blood by massaging the intact chest. A safe and effective method of "massaging the heart" without thoracotomy was developed. Adequate circulation for periods as long as 30 minutes was easily maintained with the dog in ventricular fibrillation. A closed-chest defibrillating shock would result in the immediate return of normal sinus rhythm in such animals.

In fig. 1 are shown sections taken from the recording of the variations in blood flow, blood pressure, and electrocardiogram of a dog whose heart

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Lecturer in Surgery (Dr. Kouwenhoven), Resident Surgeon (Dr. Jude), and Assistant in Surgery (Mr. Knickerbocker), Johns Hopkins University School of Medicine.

was in ventricular fibrillation for eight minutes. Simultaneously recorded on a four-channel recorder were the blood flow in a carotid artery, the instantaneous and average pressures in a femoral artery, and the cardiogram. The tracings in the first column of figure 1 are the normal values of these respective phenomena immediately before fibrillation was induced by a 110-volt shock. The second column shows the build-up of blood flow and pressures that took place when closed-chest cardiac massage was started, one minute after the onset of fibrillation. The third column is a record of what took place about seven minutes later. Note that vigorous fibrillation has been maintained throughout the entire period. The fourth and last column shows the immediate return of normal sinus rhythm when the closed chest defibrillator shock was given. The electrocardiograph was temporarily disconnected when the counter shock was applied.

Method.—The method of closed-chest cardiac massage developed during these animal studies is simple to apply; it is one that needs no complex equipment. Only the human hand is required. The principle of the method as applied to man is readily seen by consideration of the anatomy of the bony thorax and its contained organs. The heart is limited anteriorly by the sternum and posteriorly by the vertebral bodies. Its lateral movement is restricted by the pericardium. Pressure on the sternum compresses the heart between it and the spine, forcing out blood. Relaxation of the pressure allows the heart to fill. The thoracic cage in unconscious and anesthetized adults is surprisingly mobile. The method of application is shown in figure 2. With the patient in a supine position, preferably on a rigid support, the heel of one hand with the other on top of it is placed on the sternum just cephalad to the xiphoid. Firm pressure is applied vertically downward about 60 times per minute. At the end of each pressure stroke the hands are lifted slightly to permit full expansion of the chest. The operator should be so positioned that he can use his body weight in applying the pressure. Sufficient pressure should be used to move the sternum 3 or 4 cm. toward the vertebral column.

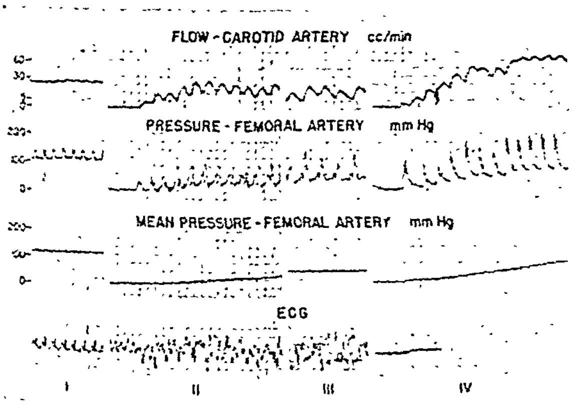

Fig. 1.—Record of blood flow, pressures, and electrocardiogram of dog whose heart was in ventricular fibrillation for eight minutes. I: normal initial values; II: start of closed-chest massage; III: seventh minute of massage; IV: closed-chest defibrillation.

Closed-chest cardiac massage provides some ventilation of the lungs, and if there is only one person present in a case of arrest, attention should be concentrated on the massage. If there are two or more persons present, one should massage the heart while the other gives mouth-to-nose respiration.

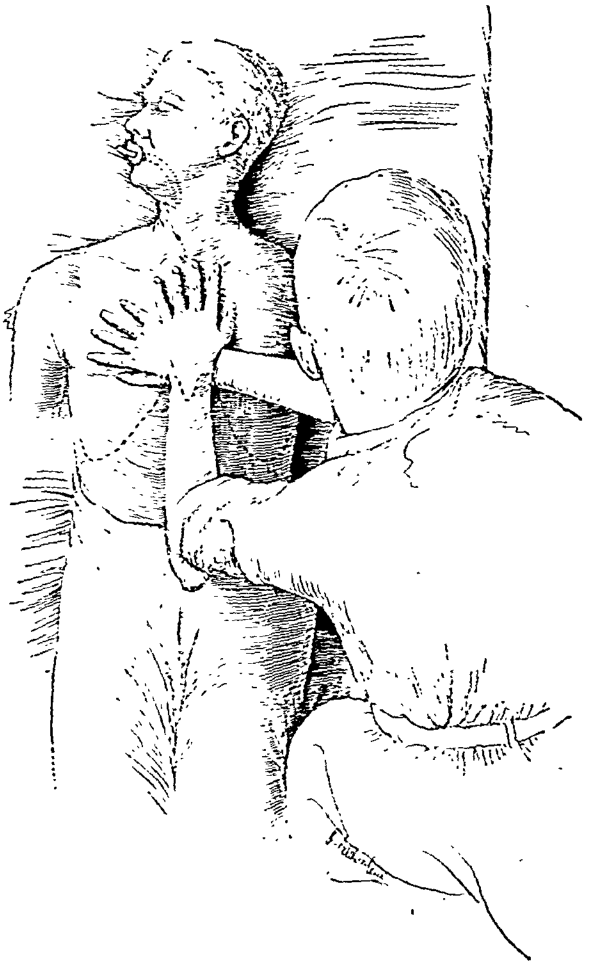

Fig 2.—Position of hands during massage of adult.

Clinical Application.—About nine months prior to time of writing, at Johns Hopkins Hospital, clinical application of closed-chest cardiac massage was successfully illustrated in a case of cardiac arrest. Initially, it was felt that the method might be useful in treating arrest in children, whose ribs are known to be flexible, but that it would not be effective in adults. This latter assumption was proved to be incorrect, since the chest of an unconscious adult was found to be remarkably flexible.

During the 10 months prior to writing this method alone has been applied on 20 patients aged from 2 months to 80 years. In 13 of these patients artificial respiration was applied simultaneously with the massage; the duration of the massage varied from less than 1 minute to 65 minutes. In seven cases records were obtained of either the blood pressure or of the electrical activity of the heart (by electrocardiogram) during the episode. Systolic pressures during massage ranged from 60 to 100 mm. Hg. Figure 3 shows the blood pressures recorded on an adult. The hearts of 3 of the 20 patients treated were in ventricular fibrillation, and all were defibrillated by a closed-chest A. C. defibrillator shock. All 20 patients were resuscitated and, at time of writing, 14 of them are alive without central nervous system damage and without undergoing thoracotomy.

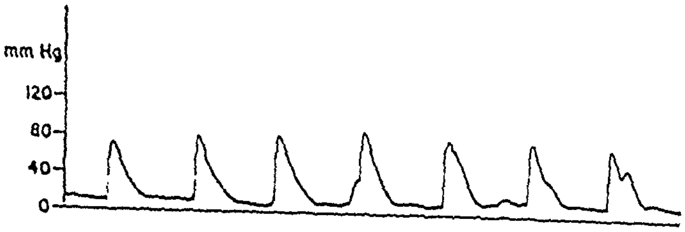

Fig. 3.—Blood pressure produced in an adult by closed-chest cardiac massage.

Report of Cases

Four cases of cardiac standstill and one case of ventricular fibrillation are reported below.

Case 1.—A 35-year-old woman was admitted in July, 1959, through the emergency room, with acute cholecystitis. After premedication with 8 mg. of morphine sulfate, 0.4 mg. of atropine, and 100 mg. of pentobarbital (Nembutal), she was taken, one and one-half hours later, to the operating room where anesthesia was induced with thiopental sodium and succinylcholine. Intubation was attempted, but difficulty was encountered, with inability to ventilate the patient. She became pulseless and cyanotic and her respirations disappeared. External cardiac massage was instituted, without artificial respiration. After two minutes a strong transthoracic pulse developed, together with spontaneous shallow respirations. Blood pressure returned to 130/80 mm. Hg and pulse to 100 beats per minute. Intubation proceeded thereafter, with some difficulty but no further cardiac problems. The patient underwent a cholecystectomy for acute hydrops of the gallbladder and had an uneventful recovery. She was discharged five days later without neurological signs or symptoms and has been entirely normal on subsequent follow-up examinations.

Case 2.—A 9-year-old boy with chronic mastoiditis was admitted and on Nov. 5, 1959, had a mastoidectomy. Postoperatively the patient was very cyanotic. Respirations stopped in the recovery room but a weak heart beat was obtainable. The child was given mouth-to-mouth respiration and cardiac assistance with external cardiac massage for about 30 seconds. He responded to this with good return of all functions and had no further difficulty. On Nov. 17, 1959, the patient was again returned to the operating room for a left mastoidectomy, after preoperative medication with 60 mg. of pentobarbital and 0.25 mg. of scopolamine. The patient was vomiting continuously on arrival in the anesthesia room, and his pulse was irregular. The induction of anesthesia was stormy because of the patient's nausea. He was given open-drop anesthesia with fluothane and intubation was performed with ease. At this point his pulse suddenly disappeared, as did the blood pressure and apical beat. Closed-chest cardiac massage was carried out for one minute and the patient responded with a good return of pulse, blood pressure, and respirations. The operation was canceled, and the patient returned to the ward. He had no further difficulties and no central nervous system damage.

Case 3.—An 80-year-old woman was admitted with a large tumor of the thyroid and had a tracheostomy with biopsy of the thyroid on Nov. 5, 1959. The diagnosis was papillary adenocarcinoma of the thyroid. She was returned to the operating room three days later for a definitive procedure after premedication with 100 mg. of pentobarbital and 0.5 mg. of atropine. She was given anesthesia with thiopental sodium and fluothane. Succinylcholine in divided doses was also given. Intubation was performed through the tracheostomy. A few minutes thereafter the blood pressure became unobtainable and the administration of fluothane was immediately stopped. There was no apical or peripheral pulse. External cardiac massage was begun immediately and carried out for a period of two minutes. Mephentermine (Wyamine), 30 mg., and phenylephrine (Neo-Synephrine) hydrochloride, 1 mg., were given intravenously. A good pulse and blood pressure returned about 90 seconds after the beginning of massage. The operation was completed without difficulty and the patient had no sign of central nervous system damage in the postoperative period.

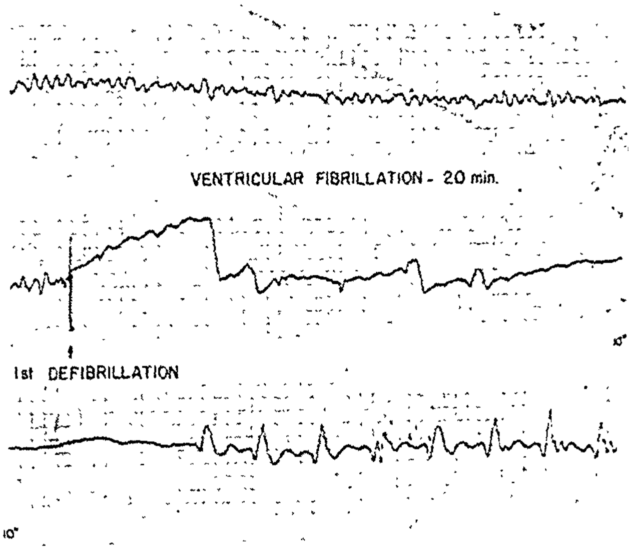

Fig. 4 (case 5).—First defibrillation shock, followed by standstill and return of fibrillation.

CASE 4.—A 12-year-old boy developed sudden cardiac arrest on Jan. 22, 1960, while undergoing an excision of a verrucus linearis of the scalp. Under thiopental and fluothane anesthesia the patient became anoxic, with an irregular pulse followed by arrest. Local infiltration with epinephrine-saline solution may have contributed. The pupils dilated and the patient was pulseless and without respiration for at least one minute before external massage was begun. After one minute of massage a good pulse and pressure returned. The operation was completed without difficulty. Postoperatively the patient had transitory blindness and bilateral Babinski reflex. Nystagmus was also present. Over 36 hours the neurological findings returned to normal. The remainder of the postoperative course was uneventful.

CASE 5.—A 45-year-old man was brought to the emergency room of the hospital with excruciating substernal chest pains radiating down both arms on Jan. 6, 1960. He was conscious when admitted. While removing his clothing, preparatory to examination, he fell to the floor. His respirations ceased, and there were no heart sounds and no pulse. The house officer immediately began closed-chest cardiac massage. An electrocardiogram was taken and showed the heart to be in ventricular fibrillation. The patient began to breathe spontaneously. Ten minutes after the start of external massage artificial respiration by endotracheal tube was first begun. External heart massage and artificial respiration were continued for 20 minutes, while a closed-chest A. C. defibrillator was being brought to the emergency room.

Two defibrillator shocks were given; the first (fig. 4) temporarily arrested the fibrillation. After the second shock (fig. 5) the heart resumed natural beats. An electrocardiographic tracing (fig. 6) taken two hours later showed an anterior myocardial infarction. Subsequent tracings confirmed the diagnosis.

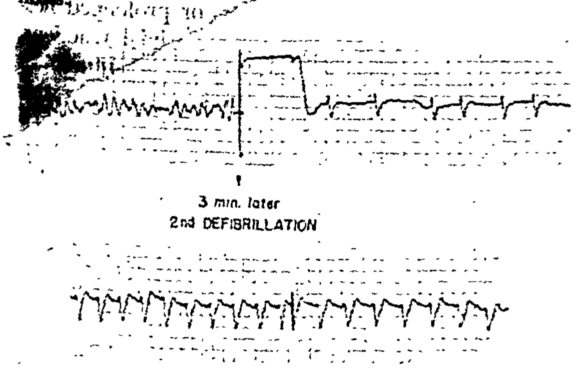

Fig. 5 (case 5).—Second defibrillation shock, followed by natural beats.

The patient had no sign of central nervous system damage, except amnesia for the period of cardiac massage plus two hours. He has followed, without incident, the usual course of treatment for myocardial infarction.

Summary

Closed-chest cardiac massage has been proved to be effective in cases of cardiac arrest. It has provided circulation adequate to maintain the heart and the central nervous system, and it has provided an opportunity to bring a defibrillator to the scene if necessary. Supportive drug treatment and other measures may be given. The necessity for a thoracotomy is eliminated. The real value of the method lies in the fact that it can be used wherever the emergency arises, whether that is in or out of the hospital.

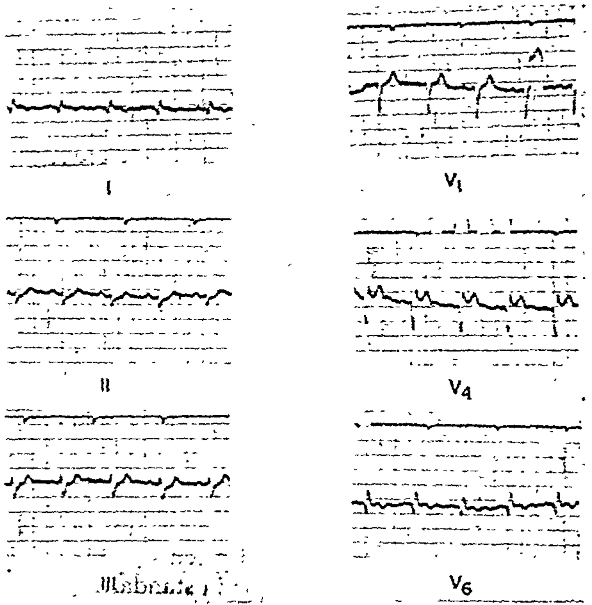

Fig. 6 (case 5).—Cardiogram taken two hours after defibrillation, showing anterior myocardial infarction.

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SURGICAL SEPSIS—REPORT ON SUBTOTAL GASTRECTOMIES

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The incidence of postoperative sepsis on a surgical service was determined because of the widespread impression that the risk of surgical sepsis is increasing. A retrospective record survey and statistical analysis of sepsis after 3,000 subtotal gastrectomies established an incidence of septic complications of 4% in the period 1941-1953. Prior to this period, when blood transfusions were not readily available, and after this period, when an increasing number of emergency subtotal gastrectomies were performed, the incidence of postoperative sepsis was greater. The clinical use of antibiotics was not synchronous with these changes. A large part of the recent rise in postoperative sepsis is a consequence of the altered case material. Numerous factors contributing to the development of sepsis require careful analysis before any one factor, such as environmental bacteria, may be held accountable.

At the Massachusetts General Hospital, in common with other surgical services throughout the country, concern has been expressed over the current rates of postoperative sepsis. The impression of more sepsis is shared by many, although facts to establish this as a widespread phenomenon are lacking. In spite of this ignorance theories are advanced to account for the assumed increase, such as the effects of the indiscriminate use of antibiotics, the results of laxity in observing time-honored aseptic techniques, the consequence of an indifferent attitude in hospital personnel, and the influence of more virulent strains of bacteria. Such speculations easily outrun proved facts concerning the incidence of postoperative sepsis. This report attempts such an evaluation by considering the postoperative course after subtotal gastrectomies performed over a 27-year period.

Techniques previously described[1] to evaluate the incidence of surgical sepsis in standard surgical procedures are extended to the operation of subtotal gastrectomy. Earlier studies have considered postoperative sepsis appearing after inguinal herniorrhaphies and abdominal hysterectomies. The background and design of these have been recorded, and only such details of organization will be discussed here as are pertinent to significant differences in execution from the earlier studies. After a presentation of the organization, the incidence of postoperative sepsis in subtotal gastrectomies, the influence of antibiotics on healing, age-specific rates, presence of staphylococci in septic cases, and the incidence of sepsis on two hospital services will be considered. An interpretation of the results in the light of this study and the two previous ones concludes the paper.

Organization of Study

Record Survey.—The data were obtained from a retrospective study of the case records of patients treated at this hospital between 1932 and 1958, inclusive. The initial survey of the records by a panel of five nurses and the subsequent review by four surgeons of all cases suggestive in any way of a septic complication and of all cases that were in any way ambiguous to the nurses were carried out in a manner identical to the previous studies. The definitions of sepsis were essentially similar to those used before and are given here for reference.

Minor sepsis refers to an inflammation of the abdominal wall incision of unusual degree, requiring local or systemic treatment or associated with a febrile response, leukocytosis, or prolonged hospitalization. Except for the most trivial reactions all that were localized around skin sutures or through-and-through sutures were placed in this category. Drainage or positive cultures were not requirements for minor sepsis. Major sepsis refers to an inflammation of the abdominal wall incision or peritoneal cavity, or both, associated with spontaneous or surgically induced purulent drainage greater than a few drops. Positive cultures were not a requirement for inclusion in this category.

Selection of Cases.—A feature of the previous studies[1] has been the uniformity of case material included in the analysis of the incidence of postoperative sepsis. This deliberate restriction has been continued, and all distal subtotal gastrectomies performed at the Massachusetts General Hospital in the 27-year period were reviewed if done for the treatment of primary gastric disease or for

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duodenal ulcer. Concomitant surgical procedures were grounds for exclusion from the study, unless the additional procedure was one of the following types: cholecystectomy, common duct exploration, splenectomy, jejunojejunostomy, small bowel resection, and appendectomy of a normal appendix. Gastric surgery for the control of bleeding esophageal varices was not included. The local excision of an ulcer, because of the limited nature of the surgical procedure, and proximal subtotal gastrectomy, because such operations commonly employ a transthoracic approach and require the time-consuming and meticulous technique of esophagoenterostomy, were excluded.

Table 1.–*Cases Removed from Subtotal Gastrectomy Series*

Cause for Removal	No.
(1) Death within 14 days of operation	
Cardiovascular or nonspecific respiratory failure, or both	26
Hemorrhage, new or persisting postoperatively	10
Pulmonary embolus	5
Cerebrovascular accident	6
Myocardial infarction	4
Ligation of common duct	3
Mesenteric thrombosis	2
Miscellaneous (pancreatitis, transfusion reaction, or renal failure)	7
Undetermined	6
Total	69
(2) Gastrointestinal suture line leak	
Duodenal stump closure (43% mortality)	40
Gastrojejunostomy (43% mortality)	14
Total	54
(3) Colon resection or colotomy performed at time of subtotal gastrectomy	55
(4) Real or potential focus of sepsis existing preoperatively (abscess at operative site, associated acute appendicitis, major pulmonary infection, or gross skin infection) or associated advanced systemic disease conducive to lowered resistance (leukemia, myloid metaplasia, or pemphigus)	52
(5) Subtotal gastrectomy for acute perforation	47
(6) Drain or jejunostomy tube in main incision	46
(7) Reexploration via main incision within 14 days of operation for resuture of abdominal wall dehiscence, for relief of gastrointestinal obstruction, or for control of postoperative hemorrhage	43
(8) Delayed closure of incision	5
(9) Trauma to incision by patient	5
(10) Ingestion of strong chemicals by patient	4
Grand Total	380

Within this selected group further refinement was achieved by excluding those cases in table 1 in which certain categories are tabulated that either could not be accurately evaluated with regard to the appearance of a septic complication or were associated with some circumstance obviously increasing the hazard of sepsis. The 380 cases tabulated were not excluded because of a septic postoperative complication but only because the patient died prematurely, as listed in category (1), making it impossible to determine whether or not sepsis would have developed had they survived, or because of unusual circumstances that could reasonably be considered as increasing the chances of a septic complication, as in categories (2) through (10).

The minimum survival time of 14 days required for inclusion in this study as a nonseptic case was chosen because 75% of the postoperative sepsis appeared within 14 days of the operation (fig. 1). None of the 69 patients who died, as shown in table 1, had a septic complication, and all cases with a septic complication associated with or contributing to a death at any time were included as examples of sepsis. None of the patients with reexplorations who were excluded had a septic complication prior to the second operation, although a number had septic incisions after the second procedure. When a reexploration was related to a septic complication, such as an incision and drainage or repair of a septic dehiscence, the case was included as a septic one. Operations with drainage of the abdominal incision, passage of an enterostomy tube through the main abdominal incision, or with secondary or delayed closure were not included. In these it was impossible to determine whether or not such incisions became septic apart from the sepsis occasioned by the bacteria transferred into the depths of the incision from the abdominal wall surface along the drain.

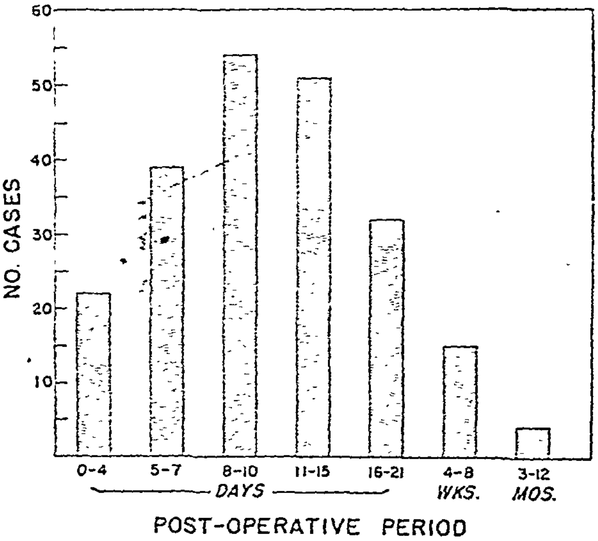

Fig. 1.–Appearance of sepsis in 217 subtotal gastrectomies.

This selection is proper to our evaluation, because the incidence of postoperative sepsis, which is a relatively rare event after clean surgery, can be grossly distorted by the inclusion of only a few septic cases which, by virtue of associated circumstances, should have been set apart from a more uniform surgical experience. Our efforts to collect a standard surgical experience over a 27-year period are patently not perfect, but the deliberate selection used is an advance over the indiscriminate bulking of widely diversified surgical operations.

Characterization of Gastrectomy Group.—The selective process yielded a group of 3,089 patients having had a subtotal gastrectomy, of which one-fifth had a gastric malignancy and the rest had peptic ulcer or other benign disease of the stomach. Slightly less than 10% had a Billroth I gastric resection, and the rest had one of the numerous modifications of a Billroth II gastric resection or, in a few instances, a more radical resection after an unsatisfactory subtotal gastrectomy. Since the incidence of postoperative sepsis was the same after each procedure, the Billroth I and II resections were combined. The average age of this predominantly male group of patients was 54 years for the nonseptic and 56 years for the septic cases. There was no essential difference in age between the patients admitted to the general hospital service and the private service, and the average age was remarkably constant over the years. This is doubtless a reflection of the stable natural history of the diseases treated which brings patients to some type of medical or surgical therapy at the same age in life today as in former years. The ages between 40 and 69 years accounted for 75% of the patients, with an additional 10% falling in both the third and the seventh decades.

The 1,622 operations performed on the private service took on the average a little more than two and one-half hours, and on the general hospital service the 1,467 operations lasted an hour longer. The administrative and clinical differences between these hospital divisions have been previously discussed in relation to postoperative sepsis.[1b] Those operations on either service which became septic averaged 10 minutes longer in duration. What relation operating time has to the appearance of postoperative sepsis, if any, is submerged in other factors to be discussed. The mortality consequent to the development of major sepsis was 17% and the median postoperative day of death in these fatalities was the 12th. The three deaths occurring after minor sepsis were not a consequence of the septic complication.

In table 2 there appears to be some diversity in the indications for operation in the group of patients included in the study. Had a larger number of cases been available, we would have preferred to select a single indication for operation and thereby achieve greater homogeneity in the surgical material reviewed. To have done this would have reduced the size of the series, so that certain statistical inferences could not have been made.

The history of perforation as an indication does not refer to an acute perforation, inasmuch as these cases were excluded as noted in table 1. The noteworthy fourfold increase in the indication of acute, massive hemorrhage and the one-and-one-half-fold increase in the indication of presumed neoplasm among the septic cases merit comment. The former indication was seen in patients contending with the stressful constellation of depleting hemorrhage, multiple transfusions, anesthesia, and subtotal gastrectomy. The latter indication was seen in patients with advanced gastric carcinoma producing chronic blood loss, malnutrition, and advanced cachexia, for which palliative resections were performed in many instances. These relations are of interest in the genesis of postoperative sepsis. The 140 patients with acute massive gastroduodenal hemorrhages had emergency subtotal gastrectomies. Such an emergency operation refers to one required to stop active hemorrhage and is precipitated by unremitting voluminous blood loss. The clinical hemorrhage, multiple transfusions, and emergency operation are continuous and overlapping events, generally occupying but a few hours. Such a train of circumstances may result in an admission to the emergency ward, or it may develop in the hospital when a patient with an eroding duodenal ulcer is under observation. Preoperatively, considerable variation in the size of the hemorrhage was noted in this group, although the rate of loss or total volume made surgery urgent, and postoperatively there was an incidence of septic complications of 24%.

Table 2.—*Indications for Operation in 3,089 Subtotal Gastrectomies*

Indication	Cases, % Nonseptic	Septic	All
Acute, massive hemorrage	3.7*	16.0*	4.6
Presumed neoplasm	24.0*	35.0*	24.4
Multiple indications (1 or more per patient)	72.3	49.0	71.0
Intractable ulcer	39.0	22.0	38.0
Chronic bleeding	25.0	26.0	25.0
Obstruction	19.0	10.0	18.0
History of perforation	1.9	1.9	1.9
Total	100.0	100.0	100.0
No. of cases	2,872	217	3,089

* Test of independence of these indications and of nonseptic and septic cases by chi-square (with Yates' adjustment) gives a value greater than 12 with $p<0.001$. Therefore, septic cases are more likely to be associated with an emergency operation for acute hemorrhage and with clinically diagnosed neoplasms than are nonseptic cases.

Follow-up Study.—The duration of the follow-up study was essentially the same over the 27 years reported, being limited to the period of hospitalization for the subtotal gastrectomy and to subsequent hospital admissions, in those patients treated on the private service, and extending, in those patients treated on the general hospital service, through the postoperative visits in the outpatient department. The review in all records was terminated at a date one year after the operation. Judging by the more complete follow-up study available in the general hospital service, 78% of the septic complications occurred in the hospital in the immediate postoperative period, with the rest appearing after discharge.

Some of these late infections necessitated a second hospitalization. It should be clear that we do not have identical follow-up studies in the two hospital divisions. This is unfortunate, but inevitable, considering the fact that private service patients are referred to the hospital staff by numerous physicians in nearby and outlying communities who provide for the long-term postoperative care and from whom it was not practical to obtain information concerning the incidence of septic complications. From the point of view of obtaining comparative statistics over the years, the follow-up study is standardized, but there presumably are, unknown to us, 10 to 15% more examples of sepsis of an inconsequential nature occurring after discharge from the private service and not severe enough to warrant readmission for treatment. Figure 1 shows the time of appearance of the septic complications.

Antibiotics.—The importance of antibiotics used as prophylaxis against postoperative sepsis was evaluated by comparing those patients who received prophylactic treatment in standard doses with such drugs as penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracycline, chloramphenicol, and erythromycin with patients to whom no antibiotics were given at any time or only after the appearance of a septic complication. There were a number of patients who had antibiotics a day or two before or a day or two after the operation, and these were excluded from the comparison inasmuch as they represent cases with a specific indication for the institution of the antibiotic therapy. This division of cases is identical with that of the previous study.[1b] A random selection of 200 cases was studied in detail to check if those patients receiving antibiotics were poor surgical risks in contrast to those not receiving antibiotics. In view of the preliminary selection described above, it is not surprising that no evidence was discovered of a bias prejudicing the healing in the groups compared.

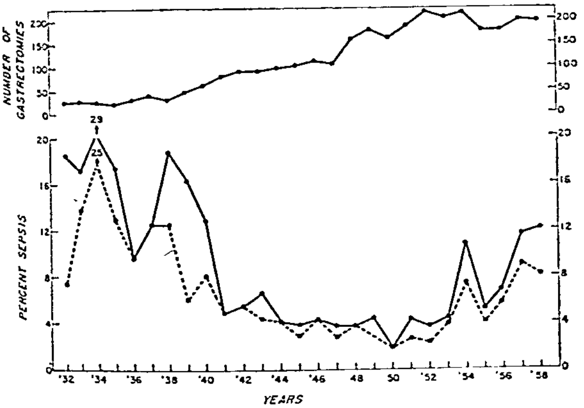

Fig. 2.—Incidence of sepsis in 3,089 subtotal gastrectomies at Massachusetts General Hospital, 1932-1958. Solid line shows total sepsis. Dotted line indicates major sepsis.

Results

The results of this investigation are set forth in tables 3 through 7 and figure 2.

Incidence of Sepsis.—The incidence of sepsis is recorded in tabular form in table 3 over the 27-year period and in figure 2 in graphic form. The data show that the incidence of sepsis of 7.0% in the entire series is largely due to major sepsis, with only one septic case in four representing minor sepsis. There appear to be three discrete periods of surgical experience, representing homogeneous and different rates of sepsis. From these three groups of annual rates we estimate the risks of sepsis and 99% fiducial limits to be as follows: for 1932-1940, 16.2%

Table 3.—*Incidence of Sepsis in 3,089 Gastrectomies at Massachusetts General Hospital, 1932—1958*

Year	Cases, No.	Sepsis, %* Minor	Major	Total
		1932—1940		
1932	27	11.1	7.41	18.5
1933	29	3.45	13.8	17.2
1934	28	3.57	25.0	28.6
1935	23	4.35	13.0	17.4
1936	31	0.00	9.67	9.67
1937	40	0.00	12.5	12.5
1938	32	6.25	12.5	18.8
1939	49	10.2	6.12	16.3
1940	62	4.84	8.06	12.9
Subtotal and Percentage of Sepsis for Period	321			16.2
		1941—1953		
1941	81	0.00	4.94	4.94
1942	91	0.00	5.49	5.49
1943	91	2.19	4.40	6.59
1944	96	0.00	4.16	4.16
1945	104	0.96	2.89	3.85
1946	115	0.00	4.35	4.35
1947	107	0.93	2.81	3.74
1948	160	0.00	3.75	3.75
1949	180	1.66	2.78	4.44
1950	162	0.00	1.85	1.85
1951	189	1.59	2.64	4.23
1952	218	1.37	2.29	3.66
1953	205	0.49	3.90	4.39
Subtotal and Percentage of Sepsis for Period	1,799			4.11
		1954—1958		
1954	216	3.24	7.41	10.65
1955	178	1.12	3.93	5.05
1956	177	1.13	5.64	6.77
1957	200	2.50	9.00	11.50
1958	198	4.03	8.08	12.11
Subtotal and Percentage of Sepsis for Period	969			9.29
Total All cases	3,089	1.75	5.28	7.03

* Chi-square values for total sepsis of individual years, when compared to that of the period percentage of total sepsis (16.2, 4.11, or 9.39), range from 0.001 in 1939 to 3.9 in 1955. Pooled chi-square values for 3 periods are in chronological order: 5.3, 4.6, and 8.5; with $0.1<p<0.99$. A test of independence of the adjoining periods and of the incidence of sepsis by chi square (with Yates' adjustment) gives values of 70 and 30 with $p<0.001$. Therefore, the above 3 periods are each homogeneous and represent significantly different risks of sepsis.

(11-22%); for 1941-1953, 4.11% (2.9-5.3%); and for 1954-1958, 9.39% (7.0-12%). Since the compilation of the bulk of this report, the figure on total sepsis for 1959 has become available and is 8.54%.

Influence of Antibiotics.—In table 4 are set forth data on the influence of antibiotics on the healing of patients having undergone subtotal gastrectomy. It is apparent that there is no beneficial effect from the use of antibiotics in reducing the incidence of sepsis as defined in this study. The lower rate of sepsis that followed the use of antibiotics is not of any compelling statistical significance.

TABLE 4.—*Influence of Antibiotics on Healing of 2,671 Subtotal Gastrectomies**

Healing of Incision	Prophylactic Antibiotics	No Antibiotics	Totals
Nonseptic	1,370	1,118	2,488
Septic	89	94	183
Totals	1,459	1,212	2,671
Sepsis, %	6.10	7.75	

* Test of independence of healing of the incisions and employment of prophylactic antibiotics by chi square (with Yates' adjustment) gives a value of 2.8 with $0.1>p>0.05$. Therefore, there is no evidence that prophylactic use of antibiotics has any influence on incidence of sepsis in healing of subtotal gastrectomies.

Age-Specific Rates of Sepsis.—In table 5 are represented the incidences of sepsis in various age groups. It is noted that the incidence of sepsis does not change in an arresting manner with the age of the patient, although there is a slight trend upward with increasing age. Again, the statistical argument for this is not particularly forceful. It is apparent that older patients are as resistant to postoperative infections as younger patients in the terms of this study, although when they have an associated disease which represents a considerable handicap to their native resistance, it is reasonable to suppose that there would be a greater incidence of all complications postoperatively, including septic ones.

TABLE 5.—*Age-Specific Rates for Sepsis in 215 Subtotal Gastrectomies*

Age, Yr.	Septic Cases, No.	Total Sepsis in Age Group, %	
0-19	2	14.3	5.04*
20-29	3	3.6	
30-39	15	5.0	
40-49	39	5.3	6.23*
50-59	63	7.0	
60-69	66	9.5	8.87*
70-79	19	6.1	
80-89	8	11.3	
90-99	0	0.0	
Total	215		

* Test of independence of adjoining grouped periods and of incidence of sepsis by chi square (with Yates' adjustment) gives values of 0.6 and 6.5. Only in comparison of middle age groups with oldest age groups is p small (<0.02). Therefore, there is only suggestive evidence of increasing age being associated with sepsis in healing of subtotal gastrectomy incisions. In 2 cases age was not accurately known. Thus, total is less than 217.

Presence of Staphylococci.—In table 6 we note that about 50% of the bacteria identified from septic cases proved to be staphylococci. The aerobic cultures were grown on blood agar plates or in beef broth. Cultures were not made from all wounds, so the collected data are weighted in favor of the extensive infections, from which cultures were more frequently made. In these data there is nothing to suggest a greater incidence of staphylococcic infection in the past nine years than previously.

Incidence of Sepsis on Two Hospital Services.—In table 7 are displayed the data concerned with the incidence of sepsis after subtotal gastrectomy on the private service and the general hospital service. The patients on these two services were of similar age, as noted previously; however, 74% of the emergency gastrectomies were performed on the general hospital service. This is consonant with the behavior of the less privileged socioeconomic class of patients encountered on the general hospital service, patients less likely to consult a physician early in the course of their disease and therefore more prone to present troublesome complications. The operations on the private service were commonly scheduled after a brief preoperative hospitalization and performed in crowded operating rooms of outmoded design. The patients on the general hospital service required more extensive studies preoperatively, unless they were admitted in emergencies, and the operations were carried out in operating rooms of modern design with efficient air-conditioning. On the whole, patients were accommodated in wards on the general hospital service and in single rooms on the private service, and this may contribute to the different rates of sepsis if cross infection is a factor in the genesis of postoperative sepsis. Because of all these individual features and others too nebulous to define, it is difficult to ascertain the causes of the

TABLE 6.—*Presence of Staphylococci Among Bacteria Cultured from 164 Septic Subtotal Gastrectomies**

Organism	1932-1950	1951-1958	Total
Staphylococcus	21	62	83
Other	28	53	81
Totals	49	115	164
Staphylococcus, %	42.8	53.8	

* Test of independence of presence of staphylococcus in flora cultured from septic cases and of two periods, before and after Jan. 1, 1951, by chi square (with Yates' adjustment) gives value of 1.2 with $0.2<p<0.3$. There is no evidence that staphylococcic sepsis is more prevalent in second period.

TABLE 7.—*Incidence of Hospital Sepsis in 3,089 Subtotal Gastrectomies on Two Hospital Services**

	Service		
Healing of Incision	General Hospital	Private	Total
Nonseptic	1,353	1,551	2,904
Septic	114	71	185
Totals	1,467	1,622	3,089
Sepsis, %	7.76	4.57	

* To permit comparison of incidence of sepsis on these two services, only sepsis appearing during hospitalization is recorded. Thus, 32 cases of sepsis disclosed in outpatient department follow-up of general hospital patients are considered as nonseptic. Test of independence of healing of incisions and of hospital service by chi square (with Yates' adjustment) gives value of 70 with $p<0.001$. Therefore, there is evidence that the two hospital services have different risks of sepsis in healing of gastrectomy incisions.

significant difference in the rate of sepsis. Although it cannot be accounted for with certainty, there is no doubt that the difference exists, and such a situation indicates the caution necessary in interpreting trends in rates of sepsis when derived from different parts of one hospital, let alone different institutions.

Comment

We have seen in table 3 and figure 2 the changing incidence of postoperative sepsis over a period of 27 years. The period 1932 through 1940 had an estimated risk of sepsis of 16%, and this declined sharply in the next 13-year period to 4.1%. This is a remarkable change in the incidence of septic complications, and scrutiny of the records and a consideration of all the currently recognized pertinent factors contributing to the genesis of sepsis lead to the conclusion that the rapidly expanding use of whole blood transfusions in the year 1941 at this hospital probably accounts for the arresting improvement. Prior to that year transfusions were given sparingly, inasmuch as the critical importance of whole blood replacement was not appreciated and the method for obtaining donors for an individual patient were cumbersome and wasteful of potential donors. The urgent demands for whole blood in 1941 resulted in the establishment of a blood bank in May, 1942, under the direction of Dr. Lamar Soutter.[2] This novel ancillary service for clinical care provided an average of one transfusion per hour for patients in this hospital during the first 10 years of its operation. Patients undergoing operations, and in particular gastrectomies, were the chief beneficiaries of the almost unlimited supply of whole blood. Surgical techniques, anesthesia, indications for the operation, operating room facilities, or the type of patient did not change abruptly in the year 1941. It is noteworthy that in the period 1937 through 1939 there was no striking change in the incidence of sepsis, even though this was a time when a number of major operations were performed in temporary quarters while the George Robert White Building was under construction. This unit was occupied in 1939, and it currently provides the modern surgical wards and operating suites for the general hospital service.

It is not surprising that the liberal use of whole blood transfusions should be followed by a decline in rates of sepsis if the experimental evidence provided by Miles and his associates[3] is recalled. These authors proved the importance of cardiovascular function in suppressing the successful "primary lodgment" of bacteria. A minimum, challenging dose of bacteria injected subcutaneously into experimental animals may be diminished a hundred-thousand-fold and yet lead to abscess formation if the animal is in a state of cardiovascular collapse for a few hours after the injection of the bacteria. The clinical parallel of a patient in postoperative shock, whose circulating blood volume is restored unaided by transfusions over many hours and who subsequently develops a septic complication, cannot be denied.

The period 1954 through 1958 had an estimated risk of sepsis of 9.4%, and this is higher than that of the previous period. This increase is largely the consequence of a greater incidence of sepsis on the general hospital service. In this five-year period the incidence of sepsis on the private service was only 5.5%. If additional facts with which to interpret this increase are sought, it may be noted in table 2 that acute, massive hemorrhage and presumed neoplasm are more frequent indications for subtotal gastrectomy in the septic than in the nonseptic cases. Furthermore, if one considers all the cases of acute massive hemorrhage that require emergency gastrectomy, it will be recalled that about one-quarter develop a septic complication. It is important to determine whether in recent years more tumor cases or more emergency cases were cared for on the general hospital service.

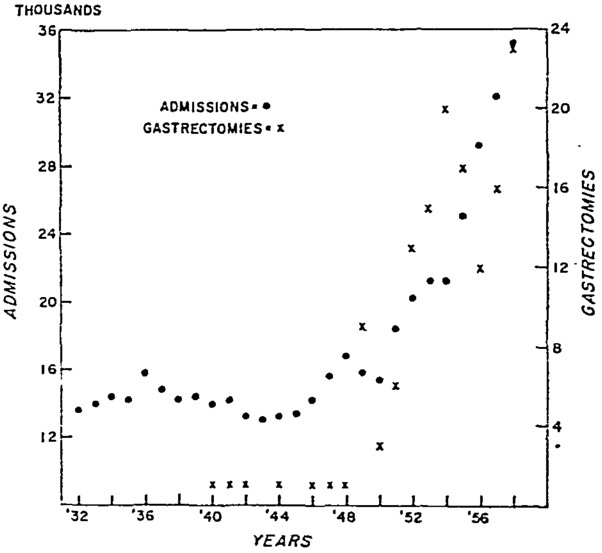

Fig. 3.—Admissions to emergency ward and emergency gastrectomies performed at Massachusetts General Hospital, 1932-1958.

A review showed that there were relatively no more patients with carcinoma of the stomach operated on during the period 1954 through 1958 than previously on the general hospital service. On the other hand, there was a noteworthy rise in the number of emergency subtotal gastrectomies that would qualify for inclusion in this study. During the past few years three-quarters of the emergency gastrectomies performed for acute massive hemorrhage have been performed on the general hospital service. The cause of this rise in the hospital experience of emergency subtotal gastrectomies and of the allocation of this type of case principally to the general hospital service is a reflection of a change in the admissions policy for the emergency ward, which doubled its patient load between 1954 and 1958. In figure 3 the number of emergency ward admissions and the number of emergency subtotal gastrectomies are plotted. It may be seen from inspection that in the period 1940 through 1948 about one emergency gastrectomy was done for every 14,000 admissions to the emergency ward. From 1949 to 1952 about one gastrectomy was done for every 2,000 admissions, and by 1958 one emergency gastrectomy was being performed for every 1,500 patients admitted to the emergency ward.

Thus both the policy change in the administration of the emergency ward and the mounting dissatisfaction with nonsurgical modes of therapy for acute gastroduodenal hemorrhage contributed to a far greater number of emergency subtotal gastrectomies than in former years. These appeared in patients from low socioeconomic groups in the greater Boston area, and, consequently, they were cared for on the general hospital service. In recent years the hospital statistics show that slightly less than one-quarter of all patients admitted to the emergency ward are admitted to the general hospital or private services. Of these patients requiring hospitalization, five-sixths are treated on the general hospital service. Although subtotal gastrectomies for massive hemorrhage had been performed for many years prior to 1940 at this hospital, these cases, relatively few in number, did not meet the criteria for inclusion in this study, principally because of their brief survival after an operation *in extremis*.[4]

If the 88 emergency cases in the period 1954 through 1958 are removed, the incidence of sepsis decreases from 9.4%, as noted in table 3, to 7.4%. However, this lower figure still represents a significant increase from the period 1941 through 1953 ($\chi^2 = 12$; $p < 0.001$). There is an increase in the sepsis associated with the emergency surgery, and this is presumably responsible for a large share of the recent increase in postoperative sepsis, but not all. The average age of the patients with septic complications in the period 1954 through 1958 is 58 years, which is somewhat older than that of the comparable patients in the whole series, 56 years. The variables introduced by the patient and his disease in the admissions from an emergency ward serving a large municipal area are complex and difficult to define or characterize in a quantitative way so as to permit a precise distinction of the patient population before and after 1954. There may well be other differences that have escaped our attention, all of which may have major or minor import for the genesis of sepsis. The private service, where the case material has been more uniform over the past 18 years, has had a relatively stable rate of sepsis compared to the general hospital service.

Furthermore, it is noteworthy that through the year 1958 the incidence of postoperative sepsis after inguinal herniorrhaphies and abdominal hysterectomies was essentially constant at this hospital.[1] Thus, the factors favoring the recent rise in sepsis on the general hospital service after subtotal gastrectomies are not common to both surgical divisions of the hospital nor are they shared by the other two operations studied. Since the personnel, including surgeons, residents, interns, anesthetists, nurses, and orderlies, are freely interchanged between the divisions; since there is no proof of any important difference in the conventional barriers to the admission of bacteria to the various operating theatres; and since anesthetic and surgical techniques are essentially similar throughout the hospital, the cumulative facts suggest that the patient and his disease may be the most significant variable to account for the rise in postoperative sepsis after subtotal gastrectomies in the past few years. The broad implications of the patient and his general condition, in contrast to environmental factors, in the genesis of clinical sepsis have been commented on by others.[5] In summary, we cannot in this retrospective record survey identify all the factors that may be causally related to the recent slight increase in postoperative sepsis. The necessities of emergency surgery are a partial explanation, and this study was not designed to refute or confirm the speculations mentioned in the introduction. Future studies with more extensive bacteriological data will be helpful.

Tables 4 through 7 present statistics on the subtotal gastrectomies that are consistent with those presented on herniorrhaphies and hysterectomies.[1b] Although the influence of antibiotics on the healing of subtotal gastrectomies is not apparent, in different circumstances antibiotics might be of critical importance, as in peripheral vascular disease where lengthy operations are performed for reconstructive arterial surgery in an extremity deprived of a normal circulation. Nothing in this report should be construed as having any direct bearing on the use of antibiotics in the treatment of established sepsis. The age-specific rates in table 5 are consistent with the earlier study in which no trend in the incidence of sepsis was seen with advancing age. There is a suggestion of a trend in the operation of subtotal gastrectomy, and the slight difference may be attributed to the fact that the inguinal herniorrhaphy and abdominal hysterectomy series was primarily composed of patients who had elective operations, whereas the subtotal gastrectomy series included patients who required an operation urgently or as an emergency measure. Consequently, patients were included in the subtotal gastrectomy series in the older age groups who had associated degenerative diseases which would have made them unsuitable candidates for an elective herniorrhaphy or hysterectomy. Table 6 shows that if we consider a relatively standardized surgical procedure, there appears to be no greater incidence of staphylococcic *contamination* after 1951 than before. This is in harmony with the comparable studies of septic herniorrhaphy and hysterectomy incisions. In table 7 a difference in the incidence of sepsis in two divisions of the same hospital is recorded, a difference, as we have seen, associated with the more numerous emergency procedures done on the general hospital service. When statistics on the incidence of sepsis are derived from two divisions of the same hospital differing in their rates of sepsis, it is important if relative annual rates are to be compared that the proportion of cases contributed by the two services remains essentially the same. This has been true in this study.

Summary and Conclusions

From a retrospective record survey of 3,089 selected subtotal gastrectomies performed over a 27-year period at the Massachusetts General Hospital the following conclusions are drawn. 1. The incidence of postoperative sepsis was 16% in the period 1932 through 1940; 4.1% in 1941 through 1953; and 9.4% in 1954 through 1958. The rise in the last five years was not seen in the incidence of postoperative sepsis after inguinal herniorrhaphies and abdominal hysterectomies. 2. The decrease in the incidence of sepsis in 1941 was concurrent with the availability of whole blood transfusions and the establishment of the hospital blood bank. 3. The increase in the incidence of sepsis beginning in 1954 was concurrent with an altered patient population seeking treatment through the hospital emergency ward facilities and requiring emergency subtotal gastrectomy in increasing numbers. 4. No single cause or group of factors has been identified to account for all the recent increase in sepsis after subtotal gastrectomy in one division of the hospital. Evidence is not available to confirm or deny the possibility that the significant variable is the patient and his disease pattern. 5. The influences of antibiotics, age, presence of staphylococci, and the incidence of sepsis on two hospital services are comparable to those in previous studies on other surgical procedures at this hospital.

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THE 1666 FIRE OF LONDON.—"This event took place the year before the fire of London, which, while it destroyed almost the whole of the City, consumed our College, and the greatest part of our Library."

One hundred and twelve folio books were saved from the flames. About ten years before this calamity, the College of Physicians had been enriched by the will of Sir Theodore Mayerne, who left his Library to them. This prosperous physician, who enjoyed the singular honour of having been physician to four kings, viz. Henry IV. of France, James I. Charles I. and Charles II. of England, died very rich. It is said he left behind him £10,000 more than Radcliffe. He was a man of singular address, and distinguished for his knowledge of chemistry and natural philosophy. The famous enamel painter Petitot, when in England, was introduced by Mayerne to Charles I. and was indebted also to him for many valuable hints as to the principal colours to be used for enamel, and the best means of vitrifying them.—The Gold-Headed Cane, London, J. Murray, 1828.

J.A.M.A., July 9, 1960

USE OF THE NEWER URICOSURIC AGENTS IN THE MANAGEMENT OF GOUT

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and
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Zoxazolamine in doses up to 125 mg., administered to patients with gout, increased the urinary excretion of uric acid and lowered the serum urate level. In some patients increasing the dosage to 250 mg. intensified these effects to the point of causing a urate crystalluria. Sulfinpyrazone and probenecid each had additive uricosuric effects when given with zoxazolamine, but all three of these uricosuric drugs (especially sulfinpyrazone) were antagonized by sodium salicylate. Given without due precautions during acute attacks of gout, the uricosuric drugs may cause exacerbations. They should be given during quiescent phases of the disease. The newer drugs are of special value in treating patients who have failed to respond to probenecid. A large fluid intake, alkalinization of the urine, and an initial low dosage of the drug helps prevent urate deposition in the urinary tract.

As a result of improved principles of management largely introduced during the past decade, patients with gout now need suffer little incapacitation. Acute attacks of gout, if frequent, can be prevented in most patients by the daily use of colchicine,[1] while the more serious aspects of the disease, consisting of bone and joint damage resulting from tophaceous urate deposits, can be prevented by the judicious use of uricosuric agents.[2] The resolution of tophaceous deposits, the prevention of growth of tophi, and a limited degree of reconstruction of joint structures have been reported after the use of probenecid in numerous clinics.[3]

Despite these favorable results in most gout patients, physicians in each clinic have encountered a few patients who have failed to respond to such therapy.[4] Prominent among the causes for such failures have been intolerance to probenecid, as shown by urticarial reaction or gastric distress, necessitating the discontinuance of the therapy, or an inadequate uricosuric response to probenecid as shown by failure to achieve near normal levels of serum uric acid which is a prerequisite to resolution of tophi. Such therapeutic failures are usually associated with severe impairment of kidney function, a relatively common complication of gout.

Newer Uricosuric Agents in Treatment of Gout

The introduction of two uricosuric drugs of greater potency, sulfinpyrazone (Anturan) and zoxazolamine (Flexin), meets a definite need for alternative uricosuric agents, and, in addition, gives promise of greatly extending the range of therapeutic effects available to the physician for treatment of tophaceous gout. The greater potency of these two agents and their additive effects when used together permit an adequate uricosuric response in all patients except those with the most severe degree of renal impairment.

Sulfinpyrazone.—Sulfinpyrazone is a chemical relative of phenylbutazone.[5] Unlike phenylbutazone, however, it has no antirheumatic activity and no sodium-retaining activity. Its uricosuric action is much greater than that of the parent compound. In contrast to phenylbutazone, it is rapidly cleared by the kidneys and its duration of action, therefore, correspondingly reduced. For this reason, multiple small doses are more effective and desirable than a single large dose during the day. Side-effects so far reported have been uncommon and consist of gastrointestinal intolerance, peptic ulcer, renal colic, and urticarial reaction.[6]

Zoxazolamine.—The uricosuric properties of zoxazolamine were discovered only after it had been in general use for several years as a muscle relaxant.[7] Like sulfinpyrazone, zoxazolamine is rapidly cleared from the blood; in figure 1, the duration of action of its uricosuric effect at various doses is shown. It is apparent that as little as 25 mg. provides a measurable uricosuria, while a single dose of 250 mg., the amount present in the commercially available tablet used as a muscle relaxant, produced a crystalluria despite the fact that the patient was drinking increased quantities of water. A similar degree and duration of uricosuric response was observed with use of sulfinpyrazone. Such remarkable uricosuric potency as these drugs exhibit, although of therapeutic value when properly used, carries also an additional hazard of precipitating uric acid in the urinary tract. The reports of a transient nephritis associated with the use of zoxazolamine may well be related, at least in part, to its uricosuric action and calls for special consideration in the clinical use of either of these drugs. Other side-effects associated with the use of zoxazolamine have been gastrointestinal discomfort, which is generally prevented by taking the drug with meals,

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From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

rare uticarial reaction, and possible hepatotoxicity reported in two patients.[8]

Salicylates.—The uricosuric action of high doses of salicylates has been known for many years. Such use of salicylates, however, has not been common medical practice for management of gout because few patients tolerate the high doses of 4-to-6 Gm. needed for this effect. Lower doses of salicylates, up to 3 Gm. per day, have been used for their analgesic action. At this dosage level, instead of promoting urate excretion, this drug produces urate retention of varying degree and counteracts the uricosuric action of probenecid to a considerable degree. Some therapeutic failures with probenecid may be attributed to the combined use of probenecid and daily doses of salicylates.

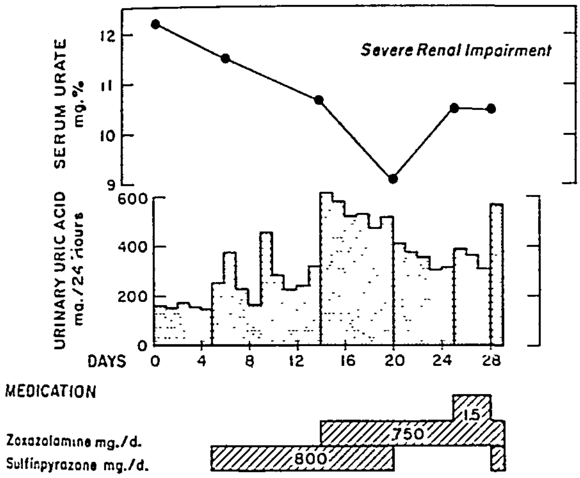

Fig. 1.—Chart showing dose response to zoxazolamine and duration of action.

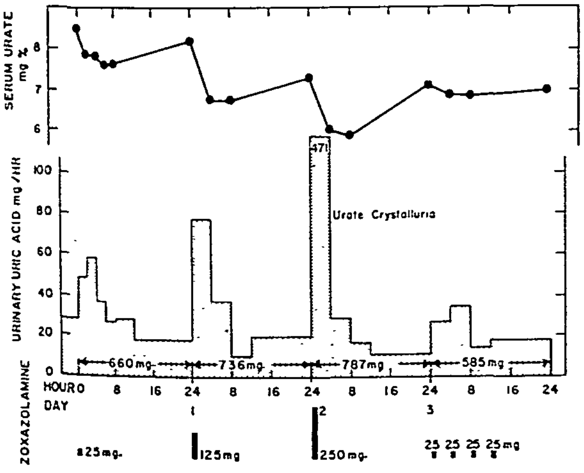

Fig. 2 (case 1).—Chart showing additive uricosuric action of sulfinpyrazone and zoxazolamine.

Combinations of Uricosuric Agents—Additive and Antagonistic Effects.—Zoxazolamine and sulfinpyrazone have a roughly comparable uricosuric action, and the maximal response obtainable with these drugs is substantially greater than that obtained with probenecid. In addition to being more potent uricosuric agents than probenecid, these two drugs when used together have an additive action which greatly extends the range of therapeutic effect available to the physician. The table and figure 2 show the effect of various combinations of uricosuric agents. The combination of zoxazolamine and sulfinpyrazone, both given in a dose of 200 mg. four times per day, produces the maximum uricosuric effect that can be obtained with the agents presently available, although such a marked uricosuric effect is seldom required. This combination is usually well tolerated by patients and has been of great value in the treatment of those problem cases of severe, long-standing, tophaceous gout associated with severe renal impairment, who have failed to obtain an adequate lowering of serum urate with a single uricosuric drug. Patients with gout and good renal function can be managed with administration of a single uricosuric agent. In most patients, probenecid, 0.5 to 3 Gm. daily, produces an adequate response.[9]

Antagonistic effects have been observed when salicylates have been given to patients receiving probenecid, zoxazolamine, or sulfinpyrazone. The antagonism of salicylates with zoxazolamine was less than with sulfinpyrazone (see the table). An increase in the dose of zoxazolamine compensated for this retention (fig. 3). The addition of a uricosuric dose of sodium salicylate to an equally effective dose of sulfinpyrazone resulted in a paradoxical urate retention, with excretion of less urate from both of these drugs together than from no drug at all. As little as 0.6 Gm. of aspirin produces a significant decrease in the uricosuria produced by sulfinpyrazone. Patients on uricosuric therapy should, therefore, be instructed to avoid completely aspirin or other drug preparations containing even small amounts of salicylate. Acetaminophen, an analgesic derivative of acetophenetidin, has demonstrated no appreciable antagonistic action to the uricosuric effect of either of these newer uricosuric agents at doses up to 0.6 Gm. four times a day.

Antagonism and Additive Action of Uricosuric Drugs

Case, No.	Uricosuric Agents	Daily Dose, Gm.	Urinary Uric Acid Excretion. Mg./Av. 24-Hr. Single Drug	Urinary Uric Acid Excretion. Mg./Av. 24-Hr. Combined Drugs
1*	Sulfinpyrazone	0.80	252	539
	Zoxazolamine	0.75	353	
2	Probenecid	3.0	576	897
	Zoxazolamine	0.75	729	
3	Probenecid	3.0	673	114
	Sodium salicylate	6.0	909	
4	Sodium salicylate	6.0	281	30
	Sulfinpyrazone	0.6	527	
5	Zoxazolamine	1.5	1195	740
	Sodium salicylate	4.8	632	

* Severe renal impairment.

Principles of Management of Gout

A fact not always remembered is that the acute attack of gouty arthritis, characteristic of the early stages of the disease, does not of itself result in permanent joint damage. Some patients will show no roentgenographic or functional evidence of joint damage despite many years of frequently recurring attacks. With the passage of time, about one-half the patients will develop evidence of tophaceous gout. The extent of such involvement, however, varies greatly, ranging from the isolated tophus in the ear to a generalized deposition of urate in cartilage, tendons, bone, and kidney. As these cystalline deposits enlarge, mechanical erosion occurs, leading to progressive bone and joint destruction and in some cases to permanent crippling.

From consideration of the variable degree to which gout is manifest, it is apparent that the treatment for any one patient with gout must be individually tailored to match the stage and severity of his particular case. The patient who has but one or two acute attacks of gout during a lifetime with a minimal degree of hyperuricemia, needs management for the acute attack only.

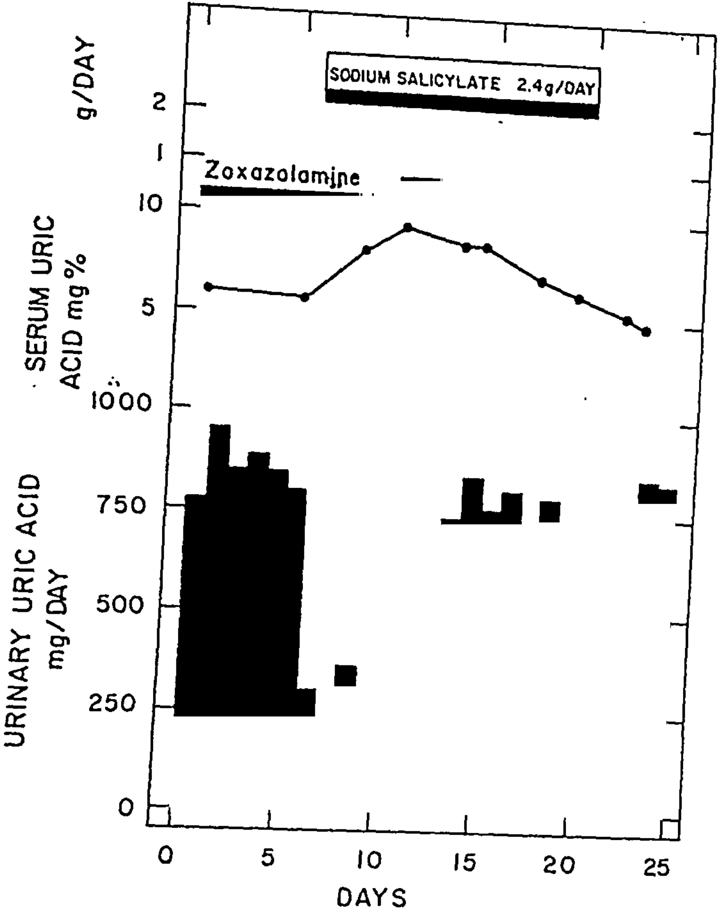

Fig. 3.—Chart showing antagonistic action of sodium salicylate on the uricosuric action of zoxazolamine; increasing dose of zoxazolamine served to compensate for suppression by sodium salicylate.

Acute Gouty Arthritis.—Colchicine remains the drug of choice for treatment of acute attacks of gout and is especially helpful if given early in the attack. At the first sign of mild symptoms suggestive of the earliest phases of an attack, the patient with known gout should be instructed to take one or two 0.5 or 0.6 mg. colchicine tablets in an effort to abort the attack. If symptoms progress, one 0.5 or 0.6 mg. tablet should be given each hour until either the joint symptoms are relieved, or toxicity manifested by nausea, vomiting, or diarrhea occurs. The tolerance of patients to colchicine varies considerably from one patient to another. In most patients the toxic symptoms appear after 6 to 10 mg. of colchicine have been given. Fortunately, a therapeutic response is often possible with smaller amounts. The diarrhea can be controlled with paregoric, 4 ml., or kaolin pectate, 30 ml., given after each loose bowel movement. Patients who experience more than one or two acute attacks per year will be benefited by a prophylactic regimen of daily doses of colchicine. To reduce the frequency and severity of attacks, the dose for chronic administration ranges from 0.6 mg. one to four times per day, depending on the frequency of symptoms and tolerance to the drug. Administration of colchicine by the intravenous route is helpful in terminating an acute attack rapidly, while generally avoiding the gastrointestinal side-effects. A dose of 2 mg. of colchicine is administered intravenously in 20 ml. of saline solution and may be followed with a second dose of 1 to 2 mg. in six hours if the response has been inadequate. No more than 5 mg. should be used for treatment of any single attack. The absence of gastrointestinal symptoms can increase the hazard of accidental overdosage, and extravasation of even small amounts of colchicine can be extremely irritating to surrounding tissues.

Attacks of acute gouty arthritis respond within a few hours to the intramuscular administration of 100 units of corticotropin (ACTH) in long-acting repository gel or zinc form. It is especially helpful in terminating severe attacks seen late in their course. Colchicine, 1 to 2 mg. per day, should be given for one to two weeks afterward to prevent an early recurrence.

Phenylbutazone is particularly useful in terminating stubborn cases that have not responded to treatment with colchicine or corticotropin. It is given in an initial dose of 400 mg., followed by 100 to 200 mg. four times daily for two to three days only. With such brief periods of administration, toxic complications are seldom seen.

Although patients with acute gout may respond to therapy with steroids, the response is generally not as consistently reliable as with other agents.

Tophaceous Gout.—Since patients with tophaceous gout characteristically show higher serum urate levels than those without such involvement, the elevated serum urate is presumed to be the primary cause of the urate deposits. The objective of treatment is to lower the serum urate levels to the normal, or near normal, range by the use of uricosuric agents and thereby allow tophaceous deposits to be dissolved away by body fluids. A normal serum urate level will also prevent the formation of new tophi. There is also a general impression that the frequency of attacks is eventually diminished concomitant with the reduction of urate levels to near normal values, despite the common clinical experience that institution of therapy with these uricosuric agents frequently provokes acute attacks in the early phase of treatment. Likewise, attempts to treat acute attacks of gout with uricosuric agents have been ineffective and are frequently accompanied by the development of a fulminating, acute attack in place of the relatively mild attack for which treatment was instituted. Institution of therapy with uricosuric agents should be deferred, therefore, until an acute attack of gout has been fully controlled.

Principles and Indications for Use of Uricosuric Agents

We believe that the following are indications for beginning therapy with a uricosuric drug: (*a*) tophaceous deposits; (*b*) gout with serum urate level, consistently above 8 mg.%; and (*c*) frequent attacks despite a maximally tolerated daily dose of colchicine.

The presence of tophaceous deposits in a gouty patient, as shown by physical or radiographic examination, is an unequivocal indication for starting therapy with a uricosuric agent. Although in theory it might seem desirable to treat all patients who show a hyperuricemia with uricosuric agents to prevent the development of gout, the relatively low incidence of about 15%[10] of clinical gout among hyperuricemic relatives of gouty persons would hardly justify such measures. Many persons go through life with a modest hyperuricemia and no ill effects. The acute attacks of gout generally precede the development of tophaceous deposits and thereby would seem to provide adequate warning in most patients. The greater incidence of urate renal lithiasis noted among relatives of gouty subjects would indicate some potential hazard in the use of uricosuric agents in such persons, unless the rigid control of factors contributing to the solubility of urate in the urine described below is followed. It is our clinical impression that patients with serum urate levels persistently less than 8 mg.% seldom show any evidence of tophaceous deposits. However, those gouty patients who consistently show urate values greater than 8 mg.%, generally show, or soon develop, tophaceous deposits and therefore require administration of uricosuric drugs. Among rheumatologists there is a general impression that when serum urate values reach near normal levels, the frequency of acute attacks is reduced. Colchicine given daily is the most effective drug for preventing acute attacks, but in those patients in whom acute attacks are not controlled in this manner, the addition of a uricosuric agent may be beneficial.

Since uricosuric agents are of no value in treating the acute attack and may frequently cause an exacerbation of acute attacks of gout, therapy with uricosuric drugs should be begun during a quiescent phase of the disease. To reduce the likelihood of such attacks during institution of therapy, daily administration of colchicine at the maximally tolerated dose, usually 0.6 mg., two to four times a day, is begun before starting therapy with uricosuric agents. Since urate deposits in the urinary tract are recognized to be a potential hazard in the use of even the relatively mild uricosuric agent probenecid, the more potent drugs carry a correspondingly greater hazard. A high fluid intake of over 3 liters per day and alkalinization of the urine increases the solubility of uric acid. For this purpose, 4 Gm. of sodium bicarbonate or trisodium citrate (one-half teaspoon), given three to four times per day, is usually adequate. In patients with hypertension or cardiac disease, use of the corresponding potassium salts allows alkalinization of the urine and avoids problems of sodium retention. From consideration of figure 1 it is apparent that a urate crystalluria in a patient with hyperuricemia can result with administration of as little as one tablet of zoxazolamine (250 mg.). With this dose, 60% of the day's uric acid was excreted within a four-hour period after ingestion, providing a graphic illustration of one of the inherent dangers in use of either of these potent uricosuric agents. That sudden excessive loads of urate may cause renal damage has long been suspected. The observation of a urate renal blockade accompanying the tremendous outpourings of uric acid sometimes associated with therapy of leukemia[11] has provided further evidence of the reality of this danger. Such sudden large urate loads on the kidney would seem to be the most likely cause of the renal damage reported to occur with use of zoxazolamine. Figure 1 also illustrates the smooth uricosuric effect obtained by giving repeated small doses of zoxazolamine. To reduce the load of uric acid presented to the kidney at any one time, these short-acting uricosuric drugs should be used in divided doses throughout the day. Since the greatest urate loads will occur during the beginning of therapy, it is important to begin at low doses and gradually increase the dose over a two-week period. For sulfinpyrazone, we begin with 50 mg. twice per day, gradually increasing to 100 mg. four times per day. For zoxazolamine, the smallest tablet commercially available is 250 mg., far greater than is required for uricosuric action. We therefore begin with one-fourth of a tablet twice per day, gradually increasing to one-half tablet four times per day over a period of two weeks. The maintenance dose of uricosuric agents should be adjusted to meet the individual needs of the patient and is governed by the serum urate levels. The objective of such therapy is to produce a normal serum urate level.

Since the serum urate level is used as a guide to therapy, a reliable method of determination is necessary. The colorimetric method of Archibald[12] has proved to be reliable for routine determinations in many laboratories. With this method the normal serum urate level for men falls below 6 mg.%. A specific enzymatic method for the determination of serum urate is also available.[13] The management of gout, therefore, becomes an individualized procedure. Since salicylates antagonize the uricosuric action of sulfinpyrazone at all dosage levels, and to some extent antagonize the action of zoxazolamine, they should be avoided when using these drugs.

The matter of dietary recommendations has been subject to considerable controversy of late. In practice we generally use a low purine diet until we are certain that the gout has come under control, both from the standpoint of serum urate levels and control of acute attacks. The greater potency of the newer uricosuric agents holds forth the hope that less rigid dietary restrictions will be needed to achieve the desired serum urate levels.

Summary

The introduction of sulfinpyrazone (Anturan) and zoxazolamine (Flexin) provides physicians with more potent drugs for increasing urate excretion. Like probenecid (Benemid) they are of no value in treating acute attacks of gouty arthritis. They are, however, very useful in preventing or treating tophaceous gout, especially in patients who fail to respond to probenecid by an adequate lowering of the serum urate level, or in whom probenecid gives rise to adverse reactions. Studies on the effect of sulfinpyrazone and zoxazolamine on urate excretion indicate that their greater potency carries a correspondingly greater danger of precipitating uric acid in the urinary tract. Such a possibility can be minimized by providing a high fluid intake, alkalinizing the urine, and beginning therapy with low doses of these drugs. Maintenance colchicine is helpful in preventing acute attacks of gout that frequently accompany the institution of therapy with uricosuric agents.

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DEVONSHIRE COLIC.—To him (Sir George Baker) the whole medical world looked up with respect, and in the treatment of any disease in the least degree unusual, if it was desired to know all that had even been said or written on the subject, from the most remote antiquity, down to the case in question, a consultation was proposed with Sir George Baker. From *his* erudition every thing was expected. He was particularly kind to the rising members of his profession, whom he encouraged and informed with great condescension and apparent interest. He was a native of Devonshire, was educated at Eton, and, afterwards, at King's College, Cambridge. The accuracy and extent of his classical learning particularly engaged the respect and admiration of the members of those institutions; and to the inhabitants of Devonshire he rendered a signal service, by pointing out the source of that species of colic and subsequent palsy, which had long been the bane of that county. It was reported at the time of the publication of his "Essay concerning the Cause of the Endemial Colic of Devonshire," that the farmers were much annoyed at his discovery; but every prejudice was at length overcome by the force of truth; and the use of lead in the construction of their cider vessels, which he clearly demonstrated to be the cause of that malady, has since been discontinued.—The Gold-Headed Cane, London, J. Murray, 1828.

PUERPERAL SEPTICEMIA AND ENDOCARDITIS CAUSED BY PSEUDOMONAS AERUGINOSA

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This report adds a 12th case to 11 documented cases of septicemia due to Pseudomonas in association with acute bacterial endocarditis. The patient, an Alaskan Indian woman, delivered a stillborn infant spontaneously under sterile controlled conditions. On the third postpartum day, treatment with procaine penicillin in doses of 600,000 (later increased to 1,000,000) units every six hours was instituted to treat infection. Pseudomonas as well as nonhemolytic staphylococci was cultured from the blood on the 30th postpartum day. Death occurred on the 59th postpartum day. Among other autopsy findings were Pseudomonas aeruginosa urinary infection, endometritis, septicemia, endocarditis, and meningitis. In addition there was adrenal necrosis with probable terminal failure. The increasing incidence of Pseudomonas aeruginosa septicemia, with acute endocarditis, is related to the use of antibiotics. The mortality of Pseudomonas septicemia is over 50%.

Since the first use of penicillin in the treatment of bacterial infection, the possibility that the bacteriostatic and bactericidal properties of antibiotics could prevent disease caused by micro-organisms has been intensively studied. In the practice of obstetrics the prophylactic use of these biologically highly active substances has been described in many conditions. Among these, the following may be listed: the prevention of subacute bacterial endocarditis in patients with preexisting rheumatic heart disease; the prevention of amnionitis and intrauterine and neonatal infection in cases of prolonged rupture of the fetal membranes prior to delivery; the prevention of recurrence of urinary tract infection; after difficult or complicated labor; after unsterile delivery; in cases of long-standing intrauterine death of the fetus; in patients with previously treated syphilis, with persistence of positive serologic test results; in patients with chronic nontuberculous lung disease; in elective induction of labor; in cesarean sections; and in treating carriers of pathogenic bacteria.

In some of the conditions described, the indications are debatable and the results often disappointing. Even in those conditions in which they are lifesaving and effective in the reduction of severe degrees of morbidity, the widespread therapeutic and prophylactic use of antibiotics has resulted to a large degree in the elimination of the antibiotic-sensitive strains of many common pathogens and the emergence of resistant variants. One significant development has been the increasing frequency of infections by organisms which rarely caused disease in the preantibiotic era. It is postulated that the antibiotics remove competitive bacteria, enabling these organisms to flourish. Among these, the gram-negative bacteria, of which the Pseudomonas group is the most important, are outstanding and among the most lethal in general circulation. This group also seems to possess increasing in vitro resistance to antibiotics.[1] Staphylococcus and Candida albicans behave like these small gram-negative rods. Furthermore, in each of these groups of organisms, changes in the epidemiology of the infections are being observed. Although formerly seen as terminal events in malignant and chronic debilitating disease[2] in older adults and in the very young, they now affect a proportionately greater segment of the young adult population.

Recent reviews of the literature on this subject show that about 160 cases of septicemia due to Pseudomonas have been reported, with a mortality of 51%.[3] In association with pregnancy, only seven previously recorded cases of septicemia due to Pseudomonas have been confirmed by positive findings of blood culture during life.[4] Even though other instances have been recorded,[5] the diagnosis of septicemia was not confirmed by blood culture. Eleven documented cases of septicemia due to Pseudomonas in association with acute bacterial endocarditis,[6] three occurring in pregnancy or the puerperium, have been reported, with a mortality of 90.9%; only one recovery has been recorded.[7] To this group we wish to add a 12th case, observed and treated on our service.

Report of a Case

A 33-year-old Alaskan Indian woman, gravida 7, para 5, was first seen in the obstetrics clinic of King County Hospital on June 8, 1958, for prenatal care; she had had no previous obstetric care. Her last menstrual period had begun on Jan. 4, 1958; the estimated date of confinement was

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Oct. 11, 1958. From a pregravid weight of 131 lb. (59.5 kg.), she had gained 9 lb. (4.1 kg.). From the fourth month of pregnancy on she had noted mild but progressive dyspnea on exertion; this was brought on by ascending five steps but disappeared quickly with rest. She had no history of cough, edema, or gastrointestinal, urinary, neuromuscular, or endocrine symptoms.

History.—In 1939, at the age of 15 years, in Alaska, she had had migrating polyarthritis with joint swelling and redness, diagnosed as acute rheumatic fever by the school medical officer and treated by bed rest for two weeks. These symptoms did not recur. At the age of 17 years she contracted pulmonary tuberculosis and at the same time was told that she had a heart murmur. The tuberculosis was treated by rest at home for two years, under the care of the Public Health Service officer, with no medication. Chest x-rays were taken quarterly. Roentgenographic examinations at yearly intervals, subsequent to the arrest of the tuberculosis, showed no evidence of reactivation of the pulmonary lesion.

Obstetric History: In 1951, at the sixth month of gestation, the membranes ruptured spontaneously. The patient was kept in a hospital in Alaska until the eighth month of gestation, when a 5-lb. 4-oz. (2,381-Gm.) live male child was delivered by cesarean section. In 1953, at full term, a 7-lb. 4-oz. (3,288.5-Gm.) male child was delivered by the normal vaginal route. There were no complications. In 1954 she had a spontaneous, complete abortion at three months' gestation. The cause was unknown. In 1955 she moved from Alaska to Seattle and was delivered at King County Hospital of a 4-lb. 5-oz. (1,956-Gm.) male infant, breech presentation, by vagina at the 33rd week of gestation. She had an uneventful postpartum course, during which she was seen in consultation in the cardiology division. The clinical diagnosis of inactive rheumatic heart disease was made. She failed to return for further investigation.

In 1956 she had a normal spontaneous vaginal delivery at 38 weeks' gestation. The baby developed jaundice at 3 days of life which disappeared without treatment. There were no other complications. In January, 1957, she had a normal spontaneous delivery at King County Hospital at 36 weeks' gestation of a 6-lb. 12-oz. (3,062-Gm.) healthy male child. At the time of delivery the pulse rate was 104 per minute, blood pressure 100/70 mm. Hg, and respirations 20 per minute. Coarse crepitant rales were heard over the right lung field posteriorly. Chest x-ray one hour post partum showed left atrial enlargement and acute pulmonary edema. Within 24 hours the acute pulmonary edema had responded completely to treatment. The electrocardiogram was within normal limits. She was treated with procaine penicillin, 1,200,000 units daily. There were no further postpartum complications and she was discharged on the fifth day post partum. During none of the three pregnancies (1955, 1956, and 1957) which were delivered at our hospital did she seek or cooperate in prenatal or postnatal investigation.

Examination in the prenatal clinic during the present pregnancy revealed a well-developed obese Indian woman in no distress. The head and neck were normal. She wore dentures. There was no peripheral edema. The blood pressure was 90/50 mm. Hg and the pulse rate 80 per minute. Examination of the heart revealed a loud mitral first sound, with presystolic and rumbling diastolic murmurs in the mitral area. There was no evidence of cardiac decompensation. On auscultation of the lungs normal vesicular breath sounds were heard. There were neither rhonchi nor crepitations. The tendon reflexes were equal and normal bilaterally. Abdominal examination showed the fundus to be 14 cm. above the symphysis pubis. Because of the early stage of gestation, the presentation was not identified and the fetal heart tones were not heard. The clinical measurements of pelvic diameters were as follows: interspinous, 25 cm.; intercristal, 32 cm.; external conjugate, 20.5 cm.; right and left oblique, each 24 cm.; diagonal conjugate, over 12.5 cm.; bituberous, 9 cm.; anterior sagittal, 7.5 cm.; posterior sagittal, 9.5 cm.; and anterioposterior, at the outlet, 13 cm.; the pubic arch measured 90 degrees. Pelvic examination showed the outlet to be parous, with a two-degree cystocele. No adnexal masses were felt. The cervix was clean and showed two healed lateral lacerations. Rectal and rectovaginal examination showed no septal or intrarectal disease.

She made two further visits to the prenatal clinic, the last being on July 11, 1958, when she complained of pain on the left side of the chest and nonproductive cough of three days' duration. The pulse rate was 108 per minute and the apex beat was 1 cm. to the left of the left midclavicular line. The cardiac murmurs were unchanged. Both lung fields were clear. The uterine fundus was 24 cm. above the symphysis pubis, and the fetal heart tones were heard in the left lower quadrant at a rate of 158 per minute. Urinalysis showed neither protein nor sugar. She was referred to the cardiology clinic, where digitalization was started on an outpatient basis. She failed to keep any further appointments. She was not seen until she reported to the emergency department of the hospital on Aug. 11, 1958, complaining of headache, gastric pain, generalized muscle pains, and abdominal cramps of 12 hours' duration. She denied having any vomiting or diarrhea. The temperature was 99.8 F (37.6 C), pulse rate 85 per minute, and respirations 14 per minute. The fetal heart tones were regular and heard in the region of the umbilicus at 112 per minute. Rectal examination revealed the presenting part to be a vertex which was not engaged and the cervix to be 3 cm. dilated. She was admitted to the obstetric service for investigation of the presenting symptoms and for observation of possible premature labor.

Physical Examination.—Physical examination on admission revealed a lethargic but cooperative obese Indian woman, complaining of lower abdominal pains and a bearing-down sensation. The blood pressure was 84/48 mm. Hg, pulse rate 112 per minute, respiratory rate 20 per minute, and temperature 100 F (37.8 C). There was no clinical anemia, jaundice, or skin rash. There was deep tenderness of the skull over both occipital areas. The ocular movements were unimpaired and normal pupillary reflexes were present. The ocular fundi were normal. The external ears and tympanic membranes were normal. The gums revealed no lesions. An area of dark discoloration, measuring 3 by 3 mm., was noted on the soft palate and the pharynx was reddened. The neck veins were not engorged. The thyroid was not palpable. The lymph nodes of the neck and axilla were not enlarged. The breasts were soft and nontender, with no palpable masses. The lungs showed normal air entry with vesicular breath sounds. No crepitations were heard. The apex beat was 2 cm. to the left of the midclavicular line. There was no palpable thrill. A rumbling grade 3 diastolic murmur was heard in the mitral area, with a presystolic crescendo. There were no murmurs in the aortic area. Examination of the abdomen revealed a healed laparotomy scar along the lower midline. The uterine fundus was palpable 22 cm. above the symphysis pubis; it was symmetrical and nontender. The liver edge was palpable 2.5 cm. below the right costal margin; it was firm, regular, and nontender. No other abdominal masses or tenderness were noted. Fetal heart tones were not heard. Rectal examination showed that the cervix was fully dilated and that the presenting vertex was 2 cm. below the level of the ischial spines in the left anterior occiput position. Neurological examination revealed the motor and sensory (pinprick and light touch) function of the cranial and peripheral nerves to be intact. There was no neck rigidity. The superficial abdominal reflexes were present, and the deep tendon reflexes were within the limits of physiologic normalcy. There was a trace of edema in both ankles. X-ray of the chest revealed the lung fields to be clear. The heart showed mitral configuration, with left atrial enlargement.

Laboratory Findings: The hematocrit reading was 39%; white blood cell count 8,900 per cubic millimeter, with a normal differential count; and result of Venereal Disease Research Laboratories test for syphilis negative. The patient's blood was found to be group O, Rh-positive. Analysis of catheterized urine showed 10 mg. of protein with neither sugar, acetone, nor formed elements.

Hospital Course

She was taken to the delivery room within two minutes of admission, where she delivered spontaneously, under sterile controlled conditions without anesthesia, a 2-lb. 14-oz. (1,304-Gm.) stillborn female child. The placenta did not immediately separate, but in the absence of bleeding and with a firm fundus no intervention was indicated. After a third stage of one hour and 13 minutes it was delivered by modified Credé procedure. The total blood loss was about 100 cc. During the delivery the pulse rate was 100 to 114 beats per minute and the blood pressure 80 to 84/40 to 44 mm. Hg; at one hour post partum they were 92 beats per minute and 80/44 mm. Hg, respectively, and the temperature was 98.6 F (37.0 C). She had no headache or muscle pains and for the rest of the day of delivery had no symptoms. Twelve hours post partum the pulse was 78 beats per minute, the venous pressure 14.8 cm. H_2O, and circulation time (arm to tongue) 16 seconds. Electrocardiogram showed normal sinus rhythm and first-degree atrioventricular block, with evidence of left atrial hypertrophy. She was given 0.5 mg. of digoxin followed by 0.25 mg. twice daily.

On the first postpartum day she vomited twice and had eight nonbloody diarrheal stools. There were no other symptoms. The temperature was 98.4 F (36.8 C) and the pulse 78 beats per minute. Examination of the chest revealed the lungs to be clear. The heart murmurs were identical with those heard on admission. The abdominal examination showed the liver to be unchanged in size or consistency. There was moderate lochia rubra. There was minimal right calf tenderness but no Homans' sign. X-ray of the chest showed dilatation of the left atrium but no evidence of pulmonary congestion. On the second postpartum day the subjective condition of the patient was satisfactory, with no change in the physical signs. The hematocrit reading was 39% and the white blood cell count 19,600 per cubic millimeter, with 76% polymorphonuclear cells, 13% stab forms, 7% lymphocytes, and 8% eosinophils. The white blood cell count was repeated, confirming the eosinophil count.

On the third postpartum day the first temperature elevation occurred, a rise to 104 F (40 C). The pulse was regular at 112 beats per minute. There was no venous distention. The lungs were clear and the heart showed the same presystolic and diastolic murmurs with a split pulmonic second sound. There was minimal neck stiffness. Findings of abdominal examination were unchanged. Speculum examination showed the vaginal walls to be clear, with no lesion of the cervix. Normal lochia rubra was seen in the cervical canal and vagina. A cervical smear was taken and the culture was subsequently reported to have grown Pseudomonas aeruginosa. Bimanual examination showed that the cervix was soft. The uterus was anterior, nontender, soft, and the size of 14 weeks' gestation. There was neither parametrial nor adnexal tenderness. The ovaries were not enlarged. Lumbar puncture was performed and 10 cc. of clear spinal fluid, with a pressure of 90 mm. H_2O, was removed. The spinal fluid contained 290 cells per cubic millimeter (95% polymorphonuclear cells) and no red blood cells, with 61 mg.% of protein and 58 mg.% of sugar. No organism was seen on gram staining. Culture of this spinal fluid revealed no growth. Urinalysis on this third postpartum day showed 10 to 15 white blood cells per high-power field and neither protein nor sugar. Simultaneous urine culture subsequently showed a moderate growth of Ps. aeruginosa and nonhemolytic streptococci. The white blood cell count was 7,900 per cubic millimeter. Procaine penicillin therapy was commenced intramuscularly in doses of 600,000 units every six hours.

On the fourth postpartum day the temperature rose to 107 F (42 C) accompanied by a shaking chill. The patient did not at first respond to verbal commands but was not comatose. Within a few minutes she was rational and did not appear ill. The pulse rate was 154 beats per minute, regular, and of good volume. General physical examination revealed the pharynx to be moderately reddened. There was no neck stiffness. The lungs were clear and cardiac signs unaltered. The abdomen was soft and the uterine fundus palpable 10 cm. above the symphysis pubis. There were no other masses and no tenderness. Bowel tones were normal. The lochia was not odorous. The legs showed no evidence of thrombophlebitis or thrombosis. Blood culture was taken at this time and later reported to have grown Ps. aeruginosa. The Pseudomonas obtained from each area was sensitive to polymyxin B and moderately sensitive to streptomycin. It was not sensitive to tetracycline, chloramphenicol, penicillin, neomycin, or nitrofurantoin (Furadantin). The Pseudomonas obtained from the blood, urine, and cervix showed virtually the same sensitivity pattern on all occasions.

On the same day, x-ray of the chest showed an enlarged left atrium and a small zone of atelectasis at the left costophrenic angle. The rest of the chest was normal. The electrocardiogram showed little change from the recording made on the day of delivery. The penicillin dosage was increased to 1,000,000 units every six hours intramuscularly and administration of chloramphenicol, 500 mg. every six hours intramuscularly, was started. This was administered orally after the first four doses.

The temperature continued to rise to 104 F two or three times daily, although the pulse rate did not rise above 100 per minute. Serum electrolyte levels on the sixth postpartum day were as follows: blood urea nitrogen, 36 mg.%, and carbon dioxide combining power 25, chloride 98, sodium 130, and potassium 4.3 mEq. per liter. The serum alkaline phosphatase level was 14.6 King-Armstrong units and the serum bilirubin level 0.4 mg.%. The total serum protein content was 6.4 Gm. and the serum transaminase level was normal at 26 units.

On the sixth postpartum day the patient was transferred to the communicable disease ward and placed in strict isolation. The drug treatment was changed to polymyxin, 50 mg. given intramuscularly four times daily, aqueous penicillin, 1,000,000 units given intravenously every four hours; and streptomycin, 1 Gm. given intramuscularly twice daily. The electrocardiogram was repeated on the 8th, 18th, 36th, and 44th postpartum days. The changes seen over the series were compatible with mild carditis. Repeated blood, urine, and spinal fluid cultures showed the organisms indicated in table 1.

The temperature continued to show daily rises up to 105 F (41 C), with concomitant rises in pulse rate up to 110 and 120 per minute. Pelvic examination on the 12th postpartum day revealed well-involuting pelvic organs, with no evidence of visible or palpable pelvic infection. Cervical smear was taken and culture was subsequently reported to show Pseudomonas. Administration of the penicillin was discontinued. On the 14th postpartum day two major epileptiform seizures occurred and were observed, each lasting approximately three minutes. They consisted of tonic and clonic movements of all the limbs with a postictal somnolent state for 20 minutes afterwards. Electroencephalogram showed the diffuse encephalopathy compatible with encephalitis or metabolic encephalopathy. She denied having headaches or visual symptoms. Neurological examination revealed only moderate neck stiffness. The thighs could be flexed to 90 degrees without symptoms. The eye movements, pupil reflexes, and ocular fundi were normal. On the 15th postpartum day administration of all drugs was discontinued except that of digoxin, 0.25 mg. twice daily, and the patient was transferred to the neuro-

Table 1.—*Results of Cultures Made in Hospital*

Postpartum Day	Site			
	Spinal Fluid	Blood	Urine	Other
3	No growth	Pseudomonas	Pseudomonas	Cervix: Pseudomonas
5	No growth	Pseudomonas	No growth	...
8	No growth	...	...	...
10	No growth	No growth	...	...
15	No growth	...	...	...
22	No growth, including TB	No growth	...	...
24	No growth	Pseudomonas	...	...
26	No growth, including TB and yeast	No growth	...	Cervix: Pseudomonas
30	No growth	Pseudomonas	Nonhemolytic staphylococci, coagulase negative	
33	No growth	...	...	...
36	...	Pseudomonas *and non*hemolytic staphylococci, coagulase positive	...	Pharynx: nonhemolytic staph*ylococci*, coagulase positive
39	No growth	Pseudomonas	...	*Stool* culture: negative
41	...	Pseudomonas	...	...
44	No growth	Pseudomonas	...	Vagina and vulva: Candida albicans
49	No growth	Pseudomonas	...	...
50	...	Pseudomonas	...	...
55	No growth	Pseudomonas	...	...
58	No growth	...	...	...
59	No growth	...	...	...

logical service. Her condition remained unchanged, with one or two elevations of temperature daily to 105 F. On the 25th postpartum day she developed transitory pain in the region of the lower dorsal spine and in the upper part of the abdomen and became lethargic. The pain was apparently not in the area of either kidney.

Examination showed mild receptive without expressive aphasia and minimal right lower facial weakness. The ocular fundi were normal. There was marked neck stiffness and the deep tendon reflexes were 3 to 4 plus, slightly more hyperactive on the right. There was a right extensor plantar response. X-ray of the chest showed a small infiltrate at the left costophrenic angle. It was thought that the lesion producing the total picture was Pseudomonas septicemia with bacterial endocarditis and multiple pyemic organ abscesses, including the brain. Intramuscular administrations of streptomycin, 0.5 mg. twice daily, and polymyxin, 25 mg. three times daily, were started. On the 26th postpartum day there was tenderness, without guarding or rigidity, in the right side of the upper part of the abdomen. There were no palpable masses, bowel tones were normal, and findings of pelvic examination were essentially normal. Culture from the cervical smear grew Pseudomonas. The blood pressure was maintained at a level of 90 to 100/60 mm. Hg until the 27th postpartum day, when it dropped to 70/40 mm. Hg. The pressure responded well to daily oral administration of 10 mg. of methoxamine and 25 mg. of prednisolone and rose to and was maintained at 100/60 mm. Hg.

On the 27th postpartum day vomiting began and persisted through the next day. The temperature was 100 F and examination of the abdomen showed slight distention but no tenderness, guarding, or palpable masses. The bowel tones were low-pitched and hyperactive. Pelvic and rectal examinations showed normal lochia alba with a nontender, mobile fundus the size of 10 weeks' gestation. Skull x-rays on this day showed no abnormality. Urine culture was taken which on the 30th postpartum day was reported to have grown nonhemolytic staphylococci, coagulase-negative, sensitive to all tested antibiotics except penicillin. Blood culture taken on the same date showed Pseudomonas. In view of the urinary findings chloramphenicol, 0.5 Gm. every six hours, was added to the antibiotic treatment. The temperature did not exceed 99 F (37 C) for the next three days, but on Sept. 14, 1958, the pyrexia returned, with low temperature elevations to 100 F. On the 35th postpartum day she complained of a sore throat and had a shaking chill. Examination revealed only hyperemia of the pharynx. Cultures of the pharynx and blood were taken and both reported later to have grown a nonhemolytic staphylococcus with the same sensitivity pattern as that previously isolated from the urine.

On the 38th postpartum day and subsequently, the temperature fluctuated from 103 to 104 F

TABLE 2.—*Results of Laboratory Tests*

Hospital Day	Hematocrit Reading, %	White Blood Cell Count,/ Cu. Mm.	Blood Urea Nitrogen Level, Mg. %	Erythrocyte Sedimentation Rates, Mm./Hour	Urinalysis White Blood or Cells/ High-Power Field	Spinal Fluid, Mg. %, White Blood Cells/Cu. Mm.
Day of delivery	39.0	8,900	...	...	None	...
Postpartum						
1	39.0	19,600	...	...	None	...
3	40.0	7,500	...	...	None	Protein 61, 290 cells
5	42.0	17,800	26	26	None	Protein 64, sugar 33, 1,000 cells
8	36.0	14,000	36	54	30 to 35	Protein 256, sugar 83, 269 cells
10	36.0	9,000	13	46	...	Protein 159, 300 cells
14	36.0	7,300	15	32	...	...
16	...	...	...	...	...	Protein 138, sugar 85; 70 cells
18	35.5	12,500	...	58	...	...
22	36.0	1,660	29	...	15 to 20	Protein 73, sugar 58, 12 cells
24	...	...	29	...	...	Protein 114, sugar 49, 750 cells
27	34.0	28,900	42	...	Innumerable	...
33	30.0	17,500	51	...	80 to 120	Protein 63, sugar 66, 6 cells
36	29.0	21,100	46	...	20 to 40	...
41	31.0	20,500	76	59	20 to 40	...
44	40.0	...	57	...	...	Protein 62, sugar 64, 12 cells
46	38.0	...	...	...	...	...
49	35.0	16,000	54	55	8 to 10	...
50	...	...	75	...	30 to 40	...
55	34.0	17,500	...	...	...	Protein 82, sugar 74, 120 cells
59	28.0	...	115	...	...	Protein 90, sugar 80, 100 cells

(39 to 40 C). The polymyxin, chloramphenicol, and streptomycin were discontinued on the 39th postpartum day and vancomycin, 1 Gm. intravenously twice daily, was given for four days, then once daily for three days. The fever was unaltered. The patient became more lethargic. Examination of the heart revealed that the murmurs which had been constant now showed slight variation. The mitral systolic murmur was increased in intensity and duration but the diastolic murmur was diminished. Table 2 shows the development of anemia, the hematocrit reading falling to 29% on the 41st postpartum day. The next day the result of the stool guaiac test was strongly positive. In view of the anemia two units of whole blood were given, raising the hematocrit reading to 40%.

On the 43rd postpartum day an area of tenderness and discoloration appeared at the tip of the patient's left fifth finger which was considered to be the result of an embolus from subacute bacterial endocarditis. The next day, pruritus vulvae and ani appeared and cultures of the vagina and vulva were taken for and grew C. albicans. On the 45th postpartum day therapy with kanamycin, 500 mg. given intramuscularly twice daily, was commenced. Streptomycin administration was continued for the rest of the hospital course and the kanamycin continued in the same dosage until the 54th postpartum day. There was no improvement in the fever nor in the gradual downhill course of the patient's condition. Neurological examination continued to reveal two to three plus nuchal rigidity, with some progression of the right-sided facial hemiparesis.

On the 52nd postpartum day the deep tendon reflexes were two plus on the left and three plus on the right. Superficial abdominal reflexes were absent. Abdominal tenderness again developed, mainly localized in the epigastrium on the right side. On the 53rd postpartum day a needle biopsy of the liver was performed under local anesthesia. Tissue was obtained which showed normal liver parenchyma but the quantity was insufficient for diagnosis. The tachycardia continued to parallel the temperature variation, the heart rate rising to 130 per minute on the 55th postpartum day, when the patient appeared to be in a critical condition. The blood pressure fell to 80/50 mm. Hg and was restored with methoxamine, 10 mg. given intramuscularly. There was total hemiparesis on the right side, with marked lethargy and confusion. An electroencephalogram on the 57th postpartum day showed focal activity in the left frontal area compatible with the diagnosis of an abscess. The patient's general condition was too poor for any surgical intervention. Prednisolone, 25 mg. daily, was given intramuscularly with no improvement. The patient's condition continued to deteriorate until Oct. 10, 1958, the 59th postpartum day, when a major convulsion occurred, followed by coma. Death occurred after 10 hours of coma.

Autopsy Findings

External examination showed no abnormalities; neither edema nor palpable lymph nodes were noted. There was moderate cyanosis of the nail beds. When the sternum was removed, the apex of the right lung was noted to be adherent to the parietal pleura. Gross and histological examinations of the lungs showed focal atelectasis and emphysema, with moderate congestion and irregular fibrosis of the alveolar walls. The heart weighed 350 Gm. The auricular appendages were free of thrombi. The wall of the left atrium was of normal thickness. The mitral valve was 0.75 cm. in diameter, barely admitting a finger tip. The posterior cusp was firm and thickened. The anterior cusp showed not only similar thickening but also a large polypoid vegetation on its superior surface, with ulceration of the cusp in the region of the vegetation. The chordae tendineae cordis were markedly thickened and shortened. The rest of the heart and its valves showed no significant changes. Section of the mitral valve showed thickening, with foci of chronic inflammatory cells and calcification. Superimposed on this was an acute endocarditis with necrosis of the valvular tissue. Gram-negative bacteria were identified on the surface of the vegetation.

The spleen weighed 135 Gm. and showed numerous septic infarcts. The splenic vein was occluded by a firm thrombus. The liver weighed 1,650 Gm. and showed two small irregular areas of acute infarction with hemorrhage and an acute inflammatory reaction. The alimentary system was otherwise normal. The combined weight of the kidneys was 275 Gm.; they were pale and showed numerous deep scars externally, with the capsules adherent at the sites of scarring. Section showed small areas of recent infarction, with old pyelonephritis and superimposed acute pyelonephritis. The uterus was the size of a 10 weeks' gestation. The endometrial lining was brown and friable. There was histological evidence of endometrial necrosis with an inflammatory reaction which was acute in some areas and chronic in others. The left adrenal gland showed extensive postmortem autolysis. Section of the right adrenal showed caseous necrosis of the medulla and part of the zona reticularis and fasciculata, with basophilic stippling of the caseous area. Acid-fast stains were normal. There was some focal cortical hyperplasia. The pituitary was grossly normal but showed foci of acute inflammation in the capsule. The brain weighed 1,250 Gm. It was sectioned coronally; the only findings of note were a 1-cm. irregular area of necrosis just beneath the cortex in the left frontal lobe and a green exudate in the tip of the posterior horn of the right lateral ventricle. Sections showed an abscess with acute inflammation in the overlying meninges. The cervical cord revealed no gross lesion but histological section showed foci of resolving meningitis. Autopsy of the baby failed to reveal the cause of death. There were neither abnormal findings nor congenital abnormalities. The final diagnosis was as follows: (1) pregnancy, intrauterine, 32 weeks' gestation; (2) normal spontaneous vaginal delivery, without anesthesia; (3) stillbirth, 2-lb. 14-oz. (1,304-Gm.) female child, Aug. 11, 1958; (4) rheumatic heart disease, with marked mitral stenosis; (5) Ps. aeruginosa urinary infection, endometritis, and septicemia; (6) acute Pseudomonas bacterial endocarditis; (7) acute and chronic pyelonephritis; (8) uremia; (9) infarcts of liver; (10) thrombosis of splenic vein with septic infarcts of spleen; (11) abscess of brain; (12) Pseudomonas meningitis; and (13) adrenal necrosis, with probable terminal adrenal failure.

Comment

This case reveals many of the features characteristic of Pseudomonas septicemia. As well as the systemic manifestations of sepsis, pyogenic emboli probably were responsible for metastatic abscesses to the central nervous system, liver, spleen, intestines, kidneys, adrenal gland, heart valves, and limbs.[8] These may develop rapidly, especially in the extremities. The secondary localizations may add to and complicate the symptoms. The persistent presence of numerous white blood cells in the cerebrospinal fluid, in the absence of culturally demonstrable organisms, has been previously recorded.[6a] In our case, gram stains were made on smears of the cerebrospinal fluid and culture attempted on 16 occasions, without demonstration of any organism, although numerous white blood cells were present. Autopsy nevertheless revealed evidence of meningitis.

Although none were present in this case, skin lesions commonly occur; in particular, dermatitis gangrenosa infantum.[9] Pharyngitis was present, but in this case did not show agranulocytic angina, which has been reported in this disease. The development of hypotensive shock is to be expected, either as an early manifestation[3] or terminally[2] when it is often profound. Although the hypotension may be brief, sustained low blood pressure and shock can be fatal complications. The precise mechanism of the shock is uncertain, but it may be due in part to the pyrogenic bacterial endotoxins (polysaccharides and phospholipid-saccharide protein complexes) and may be increased by large doses of antibiotics (Jarisch-Herxheimer reaction).

It is difficult to assess accurately the part played by adrenal insufficiency in producing or contributing to the shock. In 17 previously recorded autopsies, hemorrhage and necrosis of the adrenal was demonstrated in only one, and a septic infarct of the adrenal in a further case.[10] In our case, adrenal necrosis was present. This may have existed prior to the Pseudomonas septicemia and may have been due to tuberculosis, although no acid-fast bacilli were seen. Culture was not obtained. The terminal hypotension in our case was apparently improved by the administration of prednisolone.

Pseudomonas produces a proteolytic enzyme which hydrolyses gelatin, fibrin, casein, and albumin. The organism tends to localize in smaller blood vessels, producing thrombosis with resultant occlusion. The combination of these factors explains the infarct-like areas of necrosis with minimal inflammatory reaction which are often seen. There is a normal antibody response and gamma globulin levels[2] have been found to be normal. Most cases of Pseudomonas septicemia are secondary to instrumentation of the bladder.[11] Other recorded routes of infection are via the placental site,[8a] lumbar puncture, intravenous procedures,[6a] and rarely the intestinal canal, where this organism may be a normal inhabitant. In our case, either the urinary tract or the placental site could have been the route of entry, inasmuch as the organism was cultured initially from both areas simultaneously.

In previously recorded cases of puerperal Pseudomonas septicemia, the interval between admission and death varied between 11 and 40 days. In our case, the interval was 59 days. This long course is typical of the disease. In a nonpregnant patient Pseudomonas septicemia lasting 18 months has been recorded.

In vitro tests show that Pseudomonas is most sensitive to polymyxin B and to a lesser degree to oxytetracycline, streptomycin, neomycin, tetracycline, and erythromycin in that order. There is little sensitivity to chlortetracycline and chloramphenicol and none to penicillin and bacitracin. The combined use of drugs is recommended, polymyxin and oxytetracycline being the best combination.[12] By eliminating competitive bacteria, the administration of ineffective antibiotics may be harmful. The use of steroid hormones is generally considered to be ineffective in the treatment of hypotensive shock, although they may help in suppressing fever, leukocytosis, and other toxic signs.[13] Animal experiments have demonstrated that large doses of cortisone do not prevent hypotension and shock caused by large amounts of meningococcic toxin. Vasoconstrictor agents are indicated for the treatment of the shock. The use of blood transfusions and plasma expanders has not altered the over-all mortality of Pseudomonas septicemia.[3a] The correction of underlying defects, surgical drainage, and, where feasible, the removal of infected foci are fundamental.[14]

The gram-negative injections reemphasize the role of aseptic technique and underline the fact that it is not to be replaced by indiscriminate use of antibiotics, which alter the normal flora and allow such organisms as Pseudomonas to flourish and demonstrate pathogenicity.

Summary

The increasing incidence of Pseudomonas aeruginosa septicemia, with acute endocarditis, is related to the use of antibiotics. In a pregnant patient, metastatic sites of infection were seen in the spleen, liver, brain, heart valves, and possibly kidneys. The mortality of Pseudomonas septicemia is

over 50%. Free drainage or removal of infected foci is indicated. Polymyxin B and oxytetracycline are recommended for specific treatment. Steroids are generally considered ineffective, although some benefit was derived in this case. The role of good aseptic technique in obstetric care as emphasized in the last century in prevention of all infection cannot be overstressed.

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STAPHYLOCOCCIC FOOD POISONING.—Staphylococcal food poisoning is overwhelmingly the most prevalent of food-borne infections in the United States. . . . Ninety-five outbreaks of staphylococcal food poisoning in 1955 and 1956, reported in the weekly communicable disease summaries issued by the Public Health Service, were surveyed. . . . In 94 out of 95 outbreaks, the vehicle of this disease was reported as cooked food, which contained large proportions of protein. . . . In 63 outbreaks, or 67%, the vehicles were food mixture such as tuna salad, turkey salad, creamed chicken, potato salad, meat loaf, chicken pie, egg salad, and cream-filled pastries. Such mixtures are usually handled extensively after cooking. . . . Leftover food was the reported vehicle of this disease in 94% of 86 outbreaks reporting this information. Unrefrigerated food was reported as the vehicle in 74 of 83 outbreaks supplying information on manner of handling food after cooking. . . .

Contrary to currently accepted theory, it is clear that outbreaks commonly occur when the food is handled cleanly by personnel who are free of infections. The widespread presence of pathogenic staphylococci among healthy persons insures widespread contamination of food regardless of care in handling. Therefore, recommendations for control of this disease have one objective: to prevent the staphylococci present in cooked protein food from forming enterotoxin. In the absence of precise knowledge, the following standards were arbitrarily chosen to protect food: 40 F as the maximum temperature for keeping cold, cooked protein food; 140 F as the minimum temperature for keeping hot, cooked protein food; 3 hours as the maximum length of time cooked protein food should be kept between 40 and 140 F.—B. E. Hodge, M.D., Control of Staphylococcal Food Poisoning, *Public Health Reports,* April, 1960.

FATAL EMBOLIZATION OF PULMONARY CAPILLARIES

REPORT OF CASE ASSOCIATED WITH ROUTINE BARIUM ENEMA

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A 76-year-old woman was to have a barium sulfate enema for diagnostic purposes. A Bardex bag was inflated and the injection was begun, but the procedure could not be completed because of pain. After the bag was removed, while the patient was attempting to defecate, she suddenly died. During the subsequent microscopic examination of tissues, a fortuitous change of illumination revealed the presence of innumerable crystalline bodies in the lumen of many of the larger pulmonary blood vessels and most of the alveolar capillaries. The cause of death therefore was massive embolization of the lungs by barium sulfate crystals. Their mode of entry into the blood vessels was not completely explained. It is conceivable that sublethal degrees of pulmonary embolization occurring in the past have been misinterpreted as emotional, reflex, or cardiovascular reactions.

The present report concerns a case of sudden death, apparently causally related to the frequently performed routine diagnostic barium enema for radiologic study of the colon. Fatal embolization by entry of barium sulfate into the venous circulation during administration of a barium enema was reported by Román, Wagner, and Steinbach [1] in 1952. Their report emphasizes the rarity of the condition. Their "careful search" of the literature yielded only one other case in which barium entered the veins in a patient with ulcerative colitis, resulting in liver abscess.[2] Our own review has failed to yield additional descriptions of this accident. Our case appears to be the second reported in which the mechanism of death was acute, massive, embolization of small pulmonary vessels.

Report of Case with Autopsy Findings

A 76-year-old woman was admitted to Rockford Memorial Hospital, Rockford, Ill., on March 31, 1958. She complained of severe upper abdominal pain of two days' duration. Pain tended to radiate to the back and was severe. A less severe episode accompanied by vomiting had occurred one month earlier. Physical examination revealed severe upper abdominal tenderness, both to the left and right of the midline, blood pressure of 205/105 mm. Hg, pulse rate of 80 per minute, and normal temperature. Bowel sounds were "good" and a few scattered rales were heard at both lung bases. Laboratory studies yielded the following data: Hemoglobin 13.9 Gm.; hematocrit reading 47%; white blood cell count 19,600 per cubic millimeter, including 87% segmented granulocytes, 8% lymphocytes, and 5% monocytes. Results of urinalysis were positive for bilirubin and urobilinogen. Blood chemistry indexes included the following values: Blood urea nitrogen 11.0 mg. per 100 ml.; total serum bilirubin 3.8 mg. per 100 ml., 84% direct; serum proteins 6.3 Gm.% (albumin 4.3 Gm., globulin 2.0 Gm.); serum amylase 56 Somogyi units; serum lipase 0.05 Comfort units; prothrombin activity 76%; thymol turbidity 0.68 McLaglan units; and alkaline phosphatase 11.7 Bodansky units. The result of the Kahn test was negative. Roentgenographic examinations of chest, gallbladder, and stomach were normal except for slight cardiac enlargement.

The patient's condition improved rapidly with bed rest and conservative management, including use of anticholinergic agents and a liberal ulcer diet. Leukocytosis and bilirubin levels fell toward normal. She was discharged on the ninth hospital day convalescing from acute pancreatitis, although laboratory findings were not typical.

History During Interval.—The patient remained well until Aug. 29, 1958, when she visited her physician, as an outpatient, complaining of constipation with the urge to defecate but no passage of stool. She was using a mild cathartic twice a week. Physical findings at that time included blood pressure of 208/94 mm. Hg, with a pulse rate of 76 per minute. Heart and lungs were essentially normal. Rectovaginal examination indicated a nodular mass of doubtful nature in the cul-de-sac. Sigmoidoscopic examination could not be carried higher. There appeared to be a firm constriction at this point, but the mucosal pattern was normal. She returned to her physician for barium enema exam-

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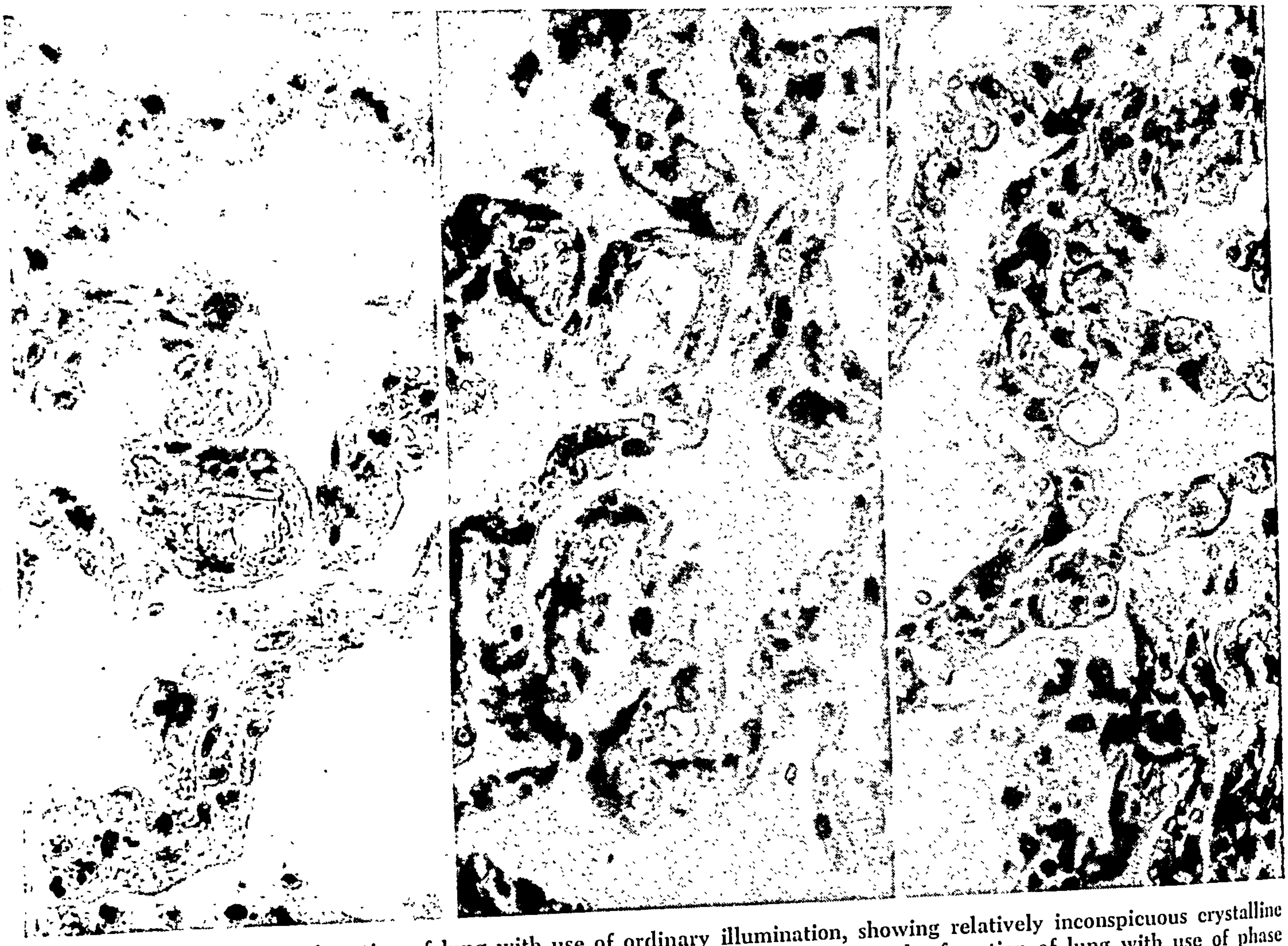
ination on Sept. 5, 1958. A Bardex bag was inflated and the injection was begun, but the patient could not tolerate the barium. The procedure was terminated. She complained of pain and while at stool just after the bag was removed, suddenly died. A small amount of fresh blood was noted on her clothing and about the anus.

A complete autopsy was performed and the following findings are abstracted as pertinent to the discussion of this case:

Abdominal Cavity.—There was no free fluid, gas, or foreign material in the abdomen. No gross evidence of trauma was present in the pelvic space or elsewhere.



Left, photomicrograph of section of lung with use of ordinary illumination, showing relatively inconspicuous crystalline inclusions in capillaries (hematoxylin-eosin stain × 340). *Middle*, photomicrograph of section of lung with use of phase contrast illumination (bright phase). Note brilliance of large and medium sized crystals (hematoxylin-eosin stain × 340). *Right*, photomicrograph of section of lung with use of phase contrast illumination (bright phase), showing medium and small crystals plugging and distending capillaries (hexatoxylin-eosin stain × 340).

Heart.—There was gross and microscopic evidence of moderate left ventricular myocardial hypertrophy. No valvular distortions were apparent. Moderate arteriosclerosis of all coronary arteries was most severe in the left, anterior, descending branch which was narrowed but not definitely occluded. Histological sections showed mild ischemic fibrosis in the high interventricular septal area.

Lungs.—Nonspecific changes in the lungs included moderate congestion of the right, middle, and lower lobes; "fluffy" consistency of both upper lobes; and minor patches of subpleural atelectasis. The critical finding in this case was revealed by viewing histological sections with reduced illumination. Most of the alveolar capillaries and many larger vessels contained crystalline bodies ranging from small amorphous granules to irregular refractile bodies reaching 10 to 12 μ in size. These findings were prominent in all lung sections (see the figure).

Kidneys.—The kidneys were normal except for gross and microscopic evidence of mild arteriosclerotic changes in interlobular arteries and replacement fibrosis of occasional glomeruli. Crystalline bodies similar to those in the lung were seen in glomerular capillaries, although smaller in size and number.

Gastrointestinal Tract.—There was no gross evidence of trauma to the mucosa of colon, sigmoid, rectum, or anus. A thin film of fresh blood was present in the lower anal canal, as well as a few clumps of white flocculent material. There was a classic 8-cm. long fusiform, rubbery enlargement of the middle of the sigmoid colon and numerous diverticula with ostiums presenting on the mucosal surface. Sections contained minor inflammatory foci about these structures but no fresh hemorrhage. A few dilated submucosal vessels, in the histological sections, showed crystalline bodies similar to those described in lung and kidneys. Hemorrhoidal varicosities were not grossly apparent.

Final Anatomic Diagnosis.—The final anatomic diagnosis was as follows: (1) massive, lethal, acute embolization of lungs by foreign bodies (barium sulfate crystals); (2) coronary arteriosclerosis, with recanalized ancient occlusion of left descending branch; (3) mild septal myocardial fibrosis; (4) moderate left ventricular myocardial hypertrophy; (5) chronic focal, interstitial pancreatitis; (6) choledocholithiasis, with partial obstruction and dilitation; (7) severe chronic diverticulitis of sigmoid colon; (8) obesity; (9) pulmonary emphysema; and (10) meningioma, right posterior occipital leptomeniges.

Comment

The pathologist, on the basis of gross pathologic changes, was of the opinion that sufficient organic disease of the heart and circulation existed to justify a belief, by exclusion, that death resulted from acute cardiac failure, possibly due to arrhythmia. The circumstances of the death led to especially careful search for visible trauma to the lower gastrointestinal tract. No such evidence was seen, and attention naturally turned to coincidental, preexisting disease.

The original impression might have stood unchallenged had it not been for the fortuitously decreased illumination while viewing the microscopic sections of the lungs. The crystalline bodies plugging the capillaries tended to disappear optically with full illumination (see figure, *left*).

The particulate matter was so striking that it seemed natural to consider the possibility of an artefact, especially since the subject had been arterially embalmed. We believe we have ruled out this possibility. The arterial injection fluid contained no visible particulate matter and no barium in sufficient amounts to spontaneously crystallize. Review of routine autopsy cases both before and after the one here reported, in which the patients also had been arterially injected, failed to show similar material. The intracapillary location of the crystals was rather sharply localized to the natural filtration beds of the circulation in the lung and kidney. The pulmonary capillary bed trapped the larger particles, only the smaller ones reaching the left side of the heart to appear in the renal gomerular tufts. Direct comparisons of the barium sulfate powder suspended in plasma were made at the same magnification as the autopsy sections. Close similarity of the particles in optical behavior, size, and shape was apparent. Chemical analyses of dried lung and kidney specimens for barium sulfate yielded values of 1.9% dried weight in lung and 1.08% of dried weight in kidney. These values are far in excess of any trace levels in normal tissues.

There was gross integrity of the mucosa of the colon in both the previously reported cases and our own. The presence of preexisting pathological change (diverticulitis), in our case, may have had a predisposing effect on the submucosal venous bed of the rectum and anal canal. The aspirating action of large venous plexuses is well known in relation to aeroembolism, which may occur with minor openings in venous channels. Each of the cases under discussion suggests the occurrence of increased pressure within the rectum at the time of the catastrophe. The previous case report stated that, "The patient began to strain down as in an attempt to defecate." Their patient was under fluoroscopy, and it was at this point that movement of barium into pelvic vessels was noted. Our patient complained of pain on inflation of the Bardex bag and the initial installation of barium. The attempt was terminated and the patient went to the bathroom and while at stool suddenly died. Some bleeding from the anus was noted at the time of death. This factor suggests the possibility of entrance of crystalline material into minute lacerations of submucosal hemorrhoidal vessels too inconspicuous to be recognized in the absence of the vascular turgescence of the living state.

On the basis of these two cases we believe the pathogenesis of this type of accident to reflect the following three factors: (1) minor and perhaps unavoidable trauma to submucosal venous channels, either normal, or somewhat hemorrhoidal in character; (2) the "aspirating" ability of venous plexuses; and (3) the existence of increased luminal pressure within the distal segment of the colon.

The paucity of case reports in the literature suggests that this is an extremely rare occurrence. We suggest the possibility that this accident may occur in somewhat higher frequency than that recorded. Conversation with radiologists and clinicians soon leaves the impression that not infrequently patients demonstrate apprehension, dyspnea, and even transient cyanosis at some phase of barium enema procedures. It is not inconceivable that sublethal embolization might occur and that these "reactions" are not all "emotional," cardiovascular, or reflex in character. The pathologist who studied the sections in the present case is impressed by the ease with which the diagnostic foreign bodies could have been overlooked, if studied under full or ordinary illumination. The tendency to emphasize the cardiovascular pathology, common to the age group undergoing this procedure, may lead to a clinical certification of death as "cardiac" without autopsy. If the possibility is not considered, even with autopsy, and the foreign bodies are not noted, a diagnosis of arteriosclerotic heart disease will almost inevitably be recorded "by exclusion."

We would like to conclude with the suggestion that the possibility of this lethal mechanism be kept in view by clinicians, radiologists, and pathologists alike, and that sudden deaths in immediate relation to instillation of crystalline, opaque, suspensions into hollow viscera, be investigated with this in mind. The possibility that the occurrence of sublethal and even fatal episodes of this nature is more frequent than the literature implies, indicates the need to develop a colloidal contrast medium compatible with entrance to the circulation in small amounts, and yet economical enough to make its use practical in the large volumes required for gastrointestinal studies.

Summary

A case of sudden death related to barium enema examination of the colon occurred. The death apparently resulted from massive embolization of the pulmonary capillary bed by barium sulfate crystals. The possibly greater incidence of sublethal and unrecognized fatal cases is suggested. Perhaps there is a need for other types of contrast mediums compatible with the probable entrance into the circulation, in some degree in an unknown percentage of examinations. A possible predisposing cause in the form of severe sigmoid diverticulitis is postulated, and it is possible that the routine use of inflatable bags in the anal .canal should be reevaluated. Recognition of the histological lesion depends on screening lung sections with reduced light.

Addendum

Another instance of sudden death in association with barium enema examination has been reported by Rosenberg and Fine,[3] since completion of this case report. In Rosenberg's and Fine's case an elderly woman also was undergoing routine examination with fluoroscopy when sudden radiation of barium occurred in a vascular pattern and was seen to enter the heart and pulmonary arteries. They also used a Bardex bag in their case. They were not able to obtain permission for autopsy, and the question of evidence of gross trauma or preexisting pathology has not been resolved.

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SHOULD THE CANCER PATIENT BE TOLD?—Among the difficult problems the surgeon must solve is how much of the patient's illness should be discussed with him. Usually the family asks that the physician deny that there is anything to worry about, and ordinarily he complies. . . . However, most medical lying is wrong, futile and often harmful. The patient is not so stupid as to be deceived. He knows that he is seriously ill, and would prefer to have the physician talk honestly with him. . . . Some may ask: "Must we always tell the truth to the very ill?" No, there is no need for forcing the truth on those who ask no questions and show no desire to discuss their illness. If an apathetic old man with an inoperable cancer of the stomach lets his sons handle his problems, if he shows no interest in the visit to the surgeon's office and asks no questions, one should not force any information on him. But when a man or woman looks the surgeon in the eye and asks what the examination showed, one feels morally and legally bound to tell the truth. Often it is highly important that a man with property know of his danger so that he can put his house in order. In brief, one must be guided by the patient's intelligence prior to answering his questions on cancer. . . . Some surgeons are performing extensive operations in an effort to cure widespread cancer. The question will often arise whether such surgery is justified in an old man or woman when the chances are that death will come anyway. It would seem that in these cases the patient should be given the facts and allowed to decide for himself. Some patients, when faced with this question, prefer to die intact, without operation. . . . Some would prefer to spend the money on the care of the family or the education of a child.—B. J. Ficarra, M.D., LL.D., Sc.D., Psychologic Management of the Aged Surgical Patient, *Journal of the American Geriatrics Society,* January, 1960.

SURGICAL TREATMENT OF BULLOUS EMPHYSEMA

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The results of treatment for bullous emphysema were studied in 37 patients. One group consisted of patients having large air cysts with poor or intermittent bronchial communication and apparently normal remaining lungs. Resection of the bulla was strikingly beneficial in some patients of this group, and eight patients were changed from severe respiratory cripples to essentially normal persons by operation. The other group consisted of patients with air cysts with poor or intermittent bronchial communication but varying degrees of emphysema in the remaining lungs. All patients with poor results were in this group. Good results depend on the selection of patients with definite symptoms, localized disease, and an emphysematous bulla or bullae occupying at least the area of one lobe of one lung. Case histories and spirometric data from four patients illustrate these points.

The treatment of patients with bullous emphysema is a subject which has met with increasing interest in recent years. Although there have been numerous papers written on the subject there has been a great deal of confusion about the method of selection of patients for surgery and conflicting reports of the results of surgical therapy. Because of the dramatic improvement surgery can effect in properly selected patients, we are presenting a group of patients treated by operation in an effort to establish certain simple criteria for operation and to show what can be expected from proper surgical procedures done in suitable patients.

The existence of cystic disease of the lung has been recognized for many years. The first report, made by Bartholinus[1] in 1687, was probably that of a congenital cyst. It was not until 1926, however, that Miller[2] described emphysematous blebs and bullae of the lung and distinguished them from congenital cysts. In recent years there have been numerous reports of the surgical treatment of various types of cystic disease of the lung,[3] but because of the varied pathology and the confusion about results the value of the treatment has been difficult to assess.

The emphysematous bullae that we are concerned with are the large acquired cysts, frequently multiple or bilateral, usually seen in men past the age of 35 years. These bullae are located deeper in the lung than blebs and have no true epithelial lining. Their bronchial communication is the same as that of the alveoli from which they are formed. In contrast, congenital bronchogenic cysts have a definite fibrous tissue wall and are lined by epithelium.

As to the cause of the formation of bullae, Miller[2] believed that they resulted from dilatation and atrophy followed by rupture of the alveolar walls and coalescence of the dilated alveoli into one another, which forms the large cysts. Clagett[3d] suggested that localized inflammatory changes may result in changes in the air ducts which result in a valvular mechanism in the bronchi. Allison[4] stated that bullous cysts may arise from overexertion, such as coughing or straining, in a patient with an inflamed or ulcerated bronchus which causes rupture of the bronchus at some weak point and escape of air into the interstitial tissues of the lung. Abbott and others,[3b] in studying a group of 294 patients with emphysema, demonstrated an almost constant history of protracted cough or chronic bronchitis. Investigation of the cause of the chronic bronchial irritation showed that the major irritants involved were tobacco and chronic suppuration. They believed that a combination of bronchospasm and edema of the bronchial tree causes partial and intermittent obstruction to air evacuation from the alveoli.

With two exceptions the patients in our series had been heavy smokers for many years. Although we do not wish to enter the smoking-cancer controversy, it is interesting to note that of the 37 patients treated for bullous emphysema 3 either had a bronchogenic carcinoma at the time they were first seen for their emphysema or developed carcinoma in the period after their operation. This does not seem surprising if one believes that bronchial irritation due to smoking is the important etiological factor in both diseases.

Report of Cases

Case 1.—A 60-year-old man whose chief complaint was progressive shortness of breath and loss of weight of 35 lb. (16 kg.) showed increase in an emphysematous bulla on the right in roentgenograms made over a period of years. Films taken shortly before operation, however, showed a pul-

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From the thoracic surgical service, Baylor University Medical Center.

monary nodule in the second right interspace which was not present on earlier films (fig. 1). At operation, in addition to the bulla, an epidermoid carcinoma was found and removed by segmental resection of the right upper lobe. Since operation the patient's breathing has improved in spite of the loss of a segment of his lung.

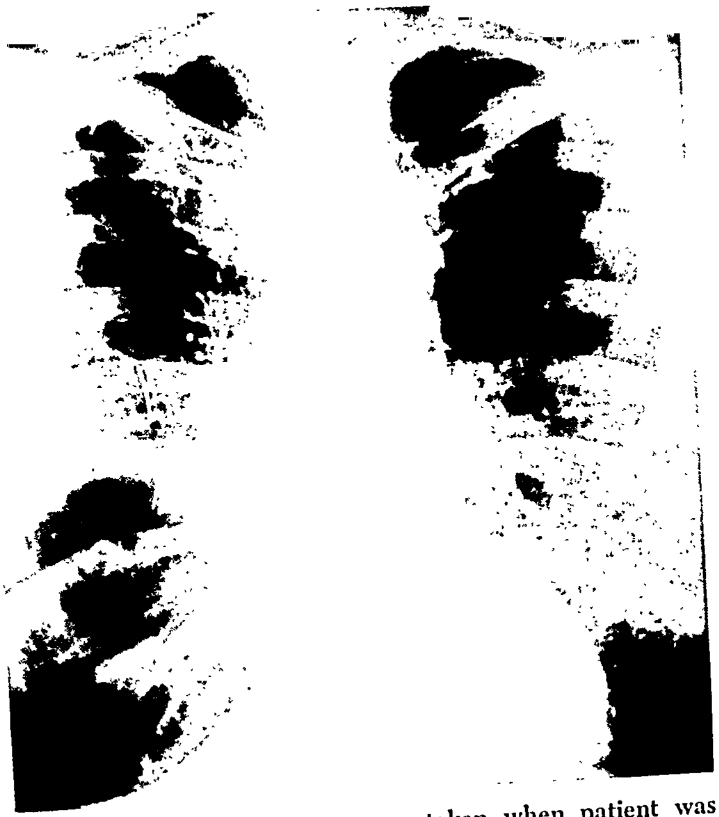

Fig. 1.—Chest roentgenogram taken when patient was seen for surgical treatment showing a large bulla in right lower lung field and also a small (1 cm.) pulmonary nodule in the second right intercostal space.

Case 2.—A 51-year-old man suffered from progressive shortness of breath, fatigue, and loss of weight. Roentgenograms taken in another city were interpreted as showing a pneumothorax (fig. 2A), and a tube was inserted (fig. 2B). When the lung did not reexpand he was sent to Dallas for treatment. Excision of the bullae was performed, and a satisfactory expansion of the lung occurred (fig. 2C).

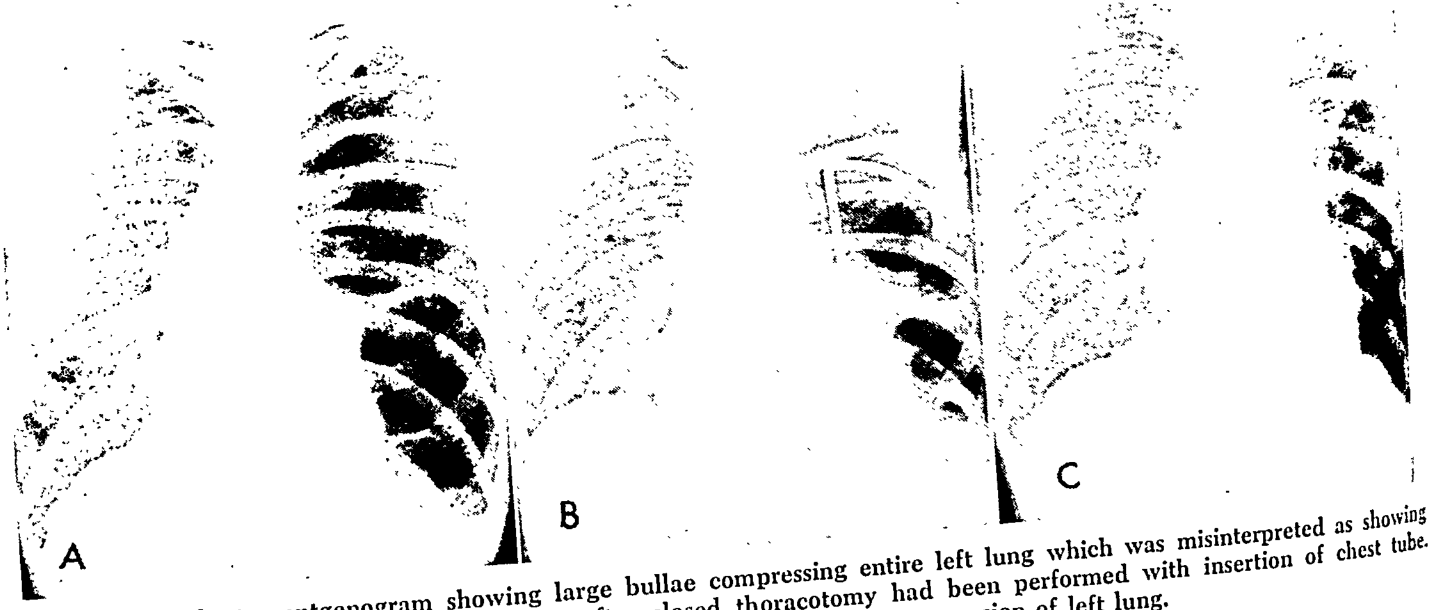

Fig. 2.—*A*, chest roentgenogram showing large bullae compressing entire left lung which was misinterpreted as showing pneumothorax. *B*, chest roentgenogram taken after closed thoracotomy had been performed with insertion of chest tube. *C*, postoperative chest roentgenogram taken after resection of bullae and reexpansion of left lung.

Case 3.—A 40-year-old man had severe progressive shortness of breath for nine months. Roentgenograms showed bilateral bullae which were resected, a year intervening between operations (fig. 3). The patient had a normal exercise tolerance at the time of this writing. Pulmonary function studies were made before and after the second operation, but not before the first, and showed a marked improvement in his vital capacity (table 1). At the time of this writing, the patient had not stopped smoking and showed no respiratory symptoms, although there was a significant obstructive component due to chronic bronchitis.

Case 4.—A 60-year-old man had marked progressive shortness of breath over a period of five years and had right heart failure when first seen. Roentgenograms of his chest showed a large bulla in the left lower lung field which had grown in size over a two-year period (fig. 4). Resection of the bulla was performed by simple excision, and resulted in the expansion of the normal-appearing left lower lobe, which had been compressed by the bulla. At the time of this writing, the patient had greatly improved clinically and had been able to return to work. Function studies showed a 50% increase in his timed vital capacity and maximum breathing capacity, although his over-all pulmonary function was very poor (table 2).

Comment

Lowell and others[5] have pointed out the connection between tension, smoking, emphysema, bronchogenic carcinoma, and peptic ulcer. From the suggestive evidence for the association between bullous emphysema and carcinoma, it would apparently behoove every physician treating patients with bullous emphysema to watch these patients most carefully for early signs of bronchogenic carcinoma.

Table 1.—*Pulmonary Function Studies Made on Patient (Case 3) Undergoing Operation for Severe Bilateral Bullous Emphysema*

	Values After First Operation*		Values After Second Operation†	
	Observed (Cc)	% Normal	Observed (Cc)	% Normal
Vital capacity	3,000	56	4,900	92
Timed vital capacity				
In 1 sec.	1,700	..	2,900	
In 2 sec.	2,400	..	..	..
In 3 sec.	2,700	52	3,900	73

* Left side.
† Right side.

Symptoms and Roentgen Findings.—The diagnosis is not a difficult one. The chief complaint is increasing shortness of breath, which usually extends over a period of years and is associated with cough, chest pain, chronic fatigue, and loss of weight. The cough may be productive of white sputum, and the chest pain is usually pleuritic in character. In our series of patients hemoptysis was uncommon. A history of repeated episodes of spontaneous pneumothorax is not unusual and constituted an indication for operation in three. Infection in a large emphysematous bulla was found in four patients who complained of fever, chest pain, and cough productive of purulent sputum. Hemorrhage into the bullae may occur but is not common and was not present in any of the patients in this series.

Table 2.—*Pulmonary Function Studies Made on Patient (Case 4) Undergoing Resection of Bulla*

	Preoperative Values			Postoperative Values	
	Predicted	Observed	% Normal	Observed	% Normal
Vital capacity	4,950 cc.	1,390 cc.	28	1,975 cc.	40
Timed vital capacity					
In 1 sec.	..	810 cc.	..	940 cc.	..
In 3 sec.	4,950 cc.	1,220 cc.	25	1,550 cc.	31
Maximum breathing					
Immediate	137.6 l./ per min.	22 l./ per min.	16	32.5 l./ per min.	24
After broncho-dilation	137.6 l./ per min.	26 l./ per min.	19	46 l./ per min.	33
Timed vital capacity after broncho-dilation					
Immediate	4,950 cc.	1,540 cc.	31	2,160 cc.	44
In 1 sec.	..	880 cc.	..	1,275 cc.	..
In 3 sec.	4,950 cc.	1,310 cc.	26	1,925 cc.	39

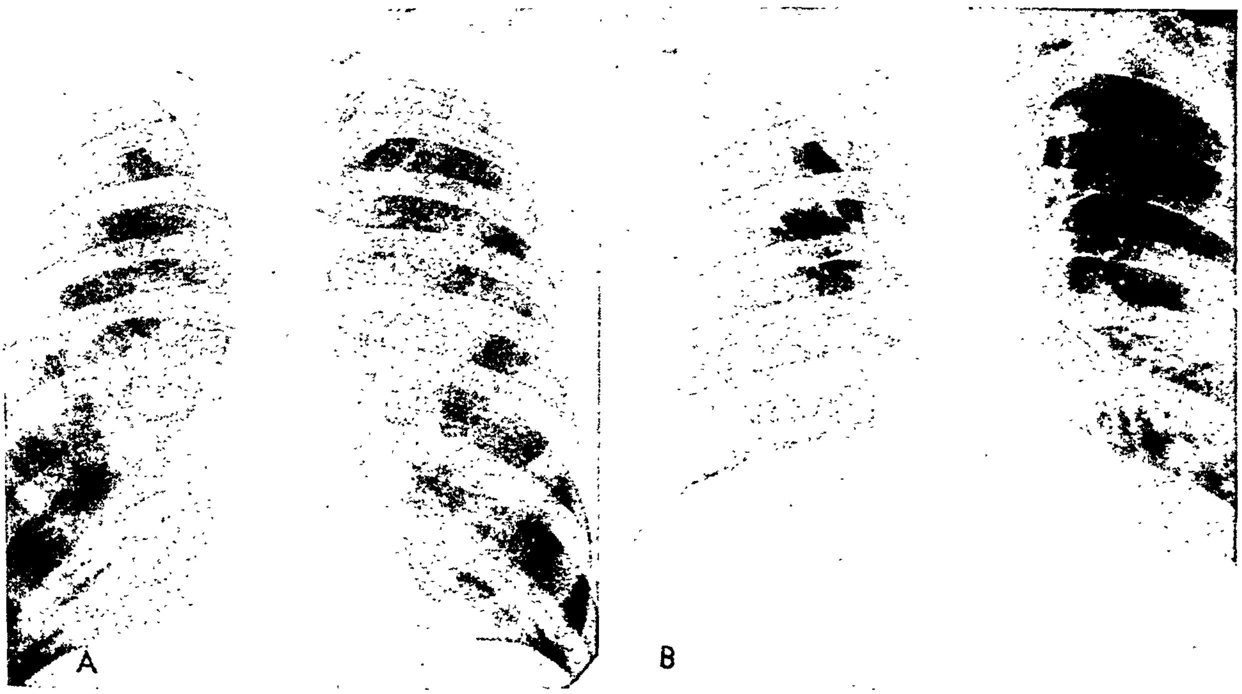

Fig. 3.—*A*, preoperative chest roentgenogram of 40-year-old man with marked bullous emphysema bilaterally. *B*, chest roentgenograms of same patient taken after bilateral resection of bullae had been performed.

Roentgenograms of the chest show large cysts on one or both sides compressing the adjacent lung tissue and even displacing the mediastinum. There is usually no difficulty in distinguishing bullae from pneumothorax because of the difference in the contour of the lung in the two conditions. Bronchograms may be of help in cases where there is some doubt and will show the bronchial tree distorted by the compression of the bulla. Diagnostic needling is a dangerous procedure and has even resulted in death in a case reported by Brock.[6]

Selection of Cases for Operation.—In general we agree with the indications for operation stated by Capel and Belcher[31] and Baldwin and others.[3k] Our criteria briefly are as follows.

The patient should be symptomatic. The presence of a large emphysematous bulla in an asymptomatic patient does not constitute an indication for operation. Many patients are known to have had had such bullae for years with no harmful effects, and at the present time there is no reliable way of predicting which of these patients will eventually need surgery. At any rate there is no harm done by waiting until symptoms develop and the need for treatment becomes certain.

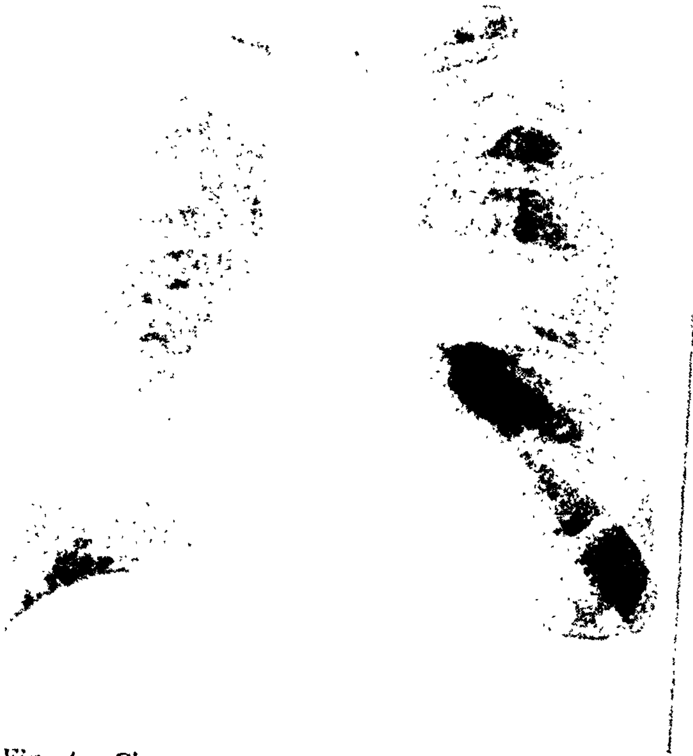

Fig. 4.—Chest roentgenogram of 60-year-old man with severe dyspnea and right heart failure. Large bulla in left lower lobe had been increasing in size during the previous two years.

The disease should be severe but localized. Patients with diffuse disease throughout both lungs will not be helped by surgery and may not even survive the operative procedure. In these patients there is no compressed normal lung tissue that can be reexpanded by removal of the bullae, so operation can accomplish little or nothing.

The emphysematous bulla should occupy at least a space as large as that of one lobe. Capel and others[31] operated only on patients with bullae occupying at least one-fourth of one lung field. Judging by size alone, no one can draw a definite line dividing bullae which are causing significant mechanical difficulties from those that are not, but from clinical experience it seems likely that symptoms in patients with bullae occupying less than one-fourth of one lung field are due to associated disease in the surrounding lung and that removal of these will not greatly benefit the patient. Recurrent spontaneous pneumothorax or infection in the bullae may constitute additional indications for surgery. Severe shortness of breath is not a contraindication to operation and may even be an urgent indication for surgical intervention.

Surgical Treatment.—At operation, the bulla or bullae are seen to be large balloon-like structures filling a large portion of the pleural space and compressing the surrounding normal lung tissue (fig. 5). Often the bulla must be deflated before its relation to the remaining lung can be seen. Resection of the bulla is made and the smallest possible amount of lung tissue is removed. In 18 patients of this series simple excision of the bullae was performed. Segmental resection was necessary in 11 patients and lobectomy in 4. Bilateral operation and an interval for recovery between operations were necessary in five patients.

A tube was inserted into six patients in whom there was an infected bulla or in patients in a dangerous condition who had extensive disease in the remaining lungs.

There have been four kinds of complications after operation. In one patient there was a persistent air leak which required closure at a second operation. One patient had a severe hemorrhage from a vascular adhesion which had to be controlled by reopening the chest. This patient also had a cardiac arrest on the operating table but was successfully resuscitated by cardiac massage and the restoration of his normal blood volume. Two patients had expansion problems and atelectasis of a portion of the remaining lung in their postoperative period. The lungs of both responded completely after appropriate treatment. There were no operative or hospital deaths.

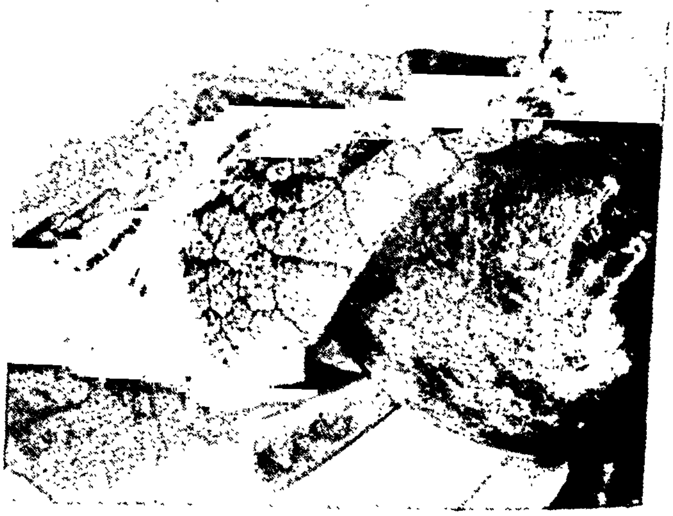

Fig. 5 (case 1).—Photograph taken at time of operation showing large balloon-like bulla attached to a relatively normal-appearing upper lobe.

Results

The results of operation have been very gratifying and even dramatic in a number of the patients in this series. There has been what we consider an excellent result in 8 of the 37 patients. These are patients who were changed from severe respiratory cripples to essentially normal persons by operation. In 18 patients operation resulted in definite improvement in their respiratory function. Three patients were improved only temporarily, and five have died from progressive disease. In three cases we have been unable to obtain any information about the patient's present status.

Baldwin and her co-workers [3k] carefully studied the results of operation in 16 cases of large pulmonary cysts or bullae which they divided into three groups according to the nature of the bronchial communication with the lesion and the functional state of the remaining lungs.

Group 1 consisted of patients with large air cysts communicating freely with the bronchial tree and associated with lungs which otherwise were apparently normal. In these patients there was considerable dead space ventilation but no interference with the excellent performance of the chest bellows and of respiratory gas exchange. In these patients surgical resection was considered optional, and in patients treated by surgery improvement in respiratory function was noted.

Group 2 consisted of patients with large air cysts with poor or intermittent bronchial communication and associated with apparently normal remaining lungs. In these patients there is ventilatory insufficiency, the extent of which depends on the size of the cyst and the pressure conditions within them. The presence of these cysts may result in collapse of the remaining normal lung. Surgery was considered mandatory in this group.

Group 3 consisted of patients who had air cysts with poor or intermittent bronchial communication associated with varying degrees of emphysema in the remaining lungs. These patients may be helped by operation if pulmonary emphysema is moderate and the arterial blood saturation normal. If emphysema is more severe and arterial blood saturation is reduced, attempts at resection do not help much and may cause death after operation.

In our series there are no patients comparable to Baldwin's group 1. Our patients with good results fall into her group 2 and those patients with poor results into group 3. We have not been able to get complete preoperative and postoperative pulmonary function studies on a majority of our patients, so the results are necessarily based on the patients' own account of their subjective symptoms and exercise tolerance and on our own clinical observations. In those patients on whom we have made function studies, operation has resulted chiefly in an increase in the timed vital capacity and in the maximum breathing capacity. It is interesting to note that a relatively small increase in the observed timed vital capacity or maximum breathing capacity can result in great clinical improvement. In some patients with poor pulmonary function a small increase may improve their function by 40 or 50%. All of the patients have been strongly urged to stop smoking, and the majority of those who have been improved by operation have also stopped smoking. We believe that their improvement has resulted from the mechanical help from removal of the bullae combined with elimination of the chronic irritant producing their bronchitis and bronchospasm.

Summary

Bullous emphysema may be treated with gratifying and even dramatic results in properly selected patients. Of the 37 patients presented 8 achieved an excellent result, 18 were improved, and 3 were improved only temporarily. Five of the patients in this group have died from progression of their disease, and in three follow-up examinations have not been made. It is believed that good results from surgical therapy will result from conservative operations performed on symptomatic patients who have localized disease and have an emphysematous bulla or bullae occupying at least the area of one lobe of one lung.

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EXSUFFLATION BELT

USE WITH INTERMITTENT POSITIVE-PRESSURE BREATHING DEVICE IN TREATMENT OF PULMONARY EMPHYSEMA

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An apparatus for use in treating pulmonary emphysema was designed to assist respiration in both the inspiratory and the expiratory phases. Air was supplied by an intermittent positive pressure breathing (IPPB) device in such a way that it flowed alternately into the patient's airways (inspiratory phase) and into an inflatable belt strapped about his body at the level of the diaphragm (expiratory phase). The apparatus was used initially on 27 patients with obstructive emphysema secondary to anthracosilicosis. Measurements of minute ventilation, tidal volume, expiratory flow rate, carbon dioxide excretion, arterial oxygen saturation, and the pCO_2 and pH of the blood showed that little, if any, objective improvement in the patients could be ascribed to the addition of the inflatable belt. Subjective improvement was reported by most patients, who thought they could breathe better.

Pulmonary emphysema is almost unsurpassed in its ability to illustrate every facet of derangement in lung function. The responsible factors are numerous and involve, in one way or another, all the major pulmonary structures. Because of the multiplicity of functions affected, the therapeutic approaches have also been varied. Most frequently treatment has been directed toward improving alveolar ventilation, since this is generally recognized as one of the basic problems in the disease. In this respect two broad therapeutic approaches have been made. One, directed toward increasing airway patency and improving the distribution of inspired air, has involved the use of expectorants, antibiotics, bronchial dilators, and intermittent positive-pressure breathing. The other, more mechanical in nature, has been designed to enhance the effectiveness of the bellows action of the thorax, and thereby cause the movement of a larger volume of air. Such measures have included breathing exercises, abdominal belts, pneumoperitoneum, and various mechanical ventilators including the intermittent positive-pressure breathing (IPPB) device. The effectiveness of any of these latter methods is proportional to its ability to bring about a significant increase in ventilation.

Recently an effort was made to combine an intermittent positive-pressure breathing device with an inflatable abdominal belt to afford a more complete approach to the treatment of obstructive emphysema. The use of the intermittent positive-pressure breathing apparatus usually provides a greater tidal volume and a more efficient distribution of air to the lung during the inspiratory phase of respiration. The abdominal belt which is inflated during expiration exerts pressure against the abdominal contents. This is believed to elevate the diaphragm, which is usually depressed in emphysema, and to aid the completeness and ease of the expiratory phase of respiration.

The device is basically an Emerson intermittent positive-pressure breathing apparatus with modifications (fig. 1). The modifications consist of a canvas belt 12 in. in width which is strapped about the upper abdomen. Inside the belt is placed a rubber bladder about 9.5 in. in diameter. The device is so constructed that on inspiration air is delivered to the patient under positive pressure in exactly the same manner as it would be in the use of any positive-pressure breathing machine. However, with the onset of expiration, when the flow of gas to the patient is interrupted, it is routed into the rubber bladder, rapidly filling it. Similarly, when the subject initiates another inspiration the flow of air to the bladder is interrupted. The latter rapidly deflates and simultaneously air is again directed to the subject. For reasons of economy, air, rather than oxygen, was used to operate the IPPB apparatus and inflate the rubber bladders. The necessary pressure was supplied by an air compresso shown in figure 1.

The belt is strapped on in such a manner that it encloses the lower portion of the rib cage and the upper abdomen. The upper edge of the belt

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From the Barton Memorial Division Jefferson Medical College Hospital.

is usually placed about 2 in. above the xiphoid process. The center of the inflatable bladder is then just below, in the epigastrium.

In order to evaluate its effectiveness in the treatment of pulmonary emphysema, the apparatus was initially used on 27 patients with obstructive emphysema secondary to anthracosilicosis. Among the parameters measured were minute ventilation, tidal volume, and expiratory flow rate. In one-third of the subjects carbon dioxide excretion, arterial saturation, pCO_2 and pH were determined as well.

Ventilation was measured first with the patients at rest. Then the intermittent positive-pressure breathing unit was attached and used in its usual manner for 20 minutes. After a 30-minute rest period the subjects were asked to use the IPPB apparatus with the belt attachment for another 20 minutes. Ventilation was measured during each breathing period. In one-half the patients the sequence was reversed and the belt attachment was used first. In nine subjects samples of arterial blood were drawn for the determination of oxygen saturation, pCO_2, and pH during rest and after each 20-minute treatment interval.

In 17 of 27 patients, or 63%, there was subjective symptomatic improvement, the patients expressing some preference for the IPPB unit with belt. This ranged from marked enthusiasm to a mild preference. Six patients, or 22%, felt that breathing was definitely worse with the belt than with the IPPB device alone. Four patients, or 15%, felt that there was no apparent difference in effect between use of the IPPB unit with or without belt.

The average ventilation at rest for the group was 10.1 liters per minute, with the IPPB apparatus it was 18.1 liters per minute, and with the IPPB device with belt it was 15.8 liters per minute. Thus, the average improvement in ventilation with the apparatus was significantly less than with the IPPB device alone. This was also true of the tidal volume which averaged 632 cc. at rest, 1,121 cc. with use of the IPPB unit, and 1,073 cc. with the attached apparatus.

The average carbon dioxide excretion was also greater with the IPPB device alone than when the abdominal belt was used. The carbon dioxide excretion at rest was 242 cc. per minute, with the IPPB device 334 cc. per minute, and with IPPB apparatus with abdominal belt 295 cc. per minute. Both the IPPB device alone and with the belt significantly lowered the pCO_2 to 31 mm. Hg and 33 mm. hg, respectively, from the average pCO_2 of 44 mm. Hg at rest.

In order to ascertain more fully the effects on expiration, flow rates were also measured. The flow rates of patients at rest averaged 32 liters a minute and increased to 63 liters a minute with use of the IPPB unit and 63 liters a minute when the belt was added.

With use of the IPPB mechanism and belt only 6 of 26 patients, or 23%, had increased ventilation and only 4 of 16, or 25%, had greater carbon dioxide excretion than with the IPPB device alone. Six of 10, or 60%, however, had a greater decrease in pCO_2 with use of the belt, and 7 of 12, or 58%, had a higher expiratory flow rate with the belt. Even in patients who did not like to use the belt there was not always correlation between the objective and the subjective results. One patient who disliked using the belt had had greater ventilation and tidal volume than with use of the IPPB apparatus alone.

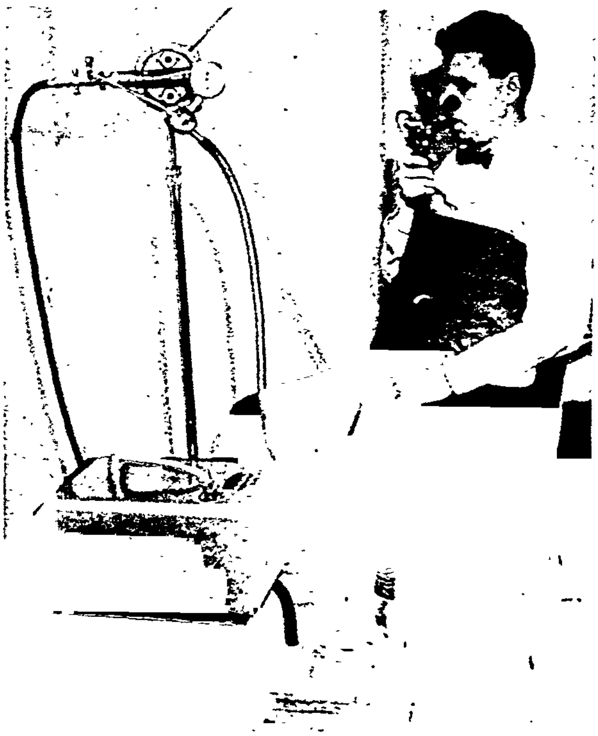

Fig. 1.—IPPB apparatus with exsufflation belt in use by patient.

Comparison of the subjective results with body surface area and body build showed no essential difference in type of response, although Gordon[1] mentioned that diaphragmatic elevation is especially valuable in patients with the long flat type of chest.

Cuirass Modification

During the course of the study it became apparent that no gross improvements in ventilatory function were achieved. The reasons for this could have been several, but we were struck by two aspects of the apparatus which could partially account for it. Initially, when the bladder was inflated beneath the canvas belt, it was believed that much of the pressure was dissipated outwardly rather than being applied against the abdomen. There also was the possibility that the bladder was too small to exert sufficient pressure. Accordingly, the abdominal belt was replaced by a firm cuirass-like form, which covered the anterior thorax from the lower axilla to the epigastrium (fig. 2*A*). The cuirass is inserted into a pocket in a wide canvas belt, which is wrapped tightly about the patient (fig. 2*B*). The inflatable bladder is then placed in the same pocket between the cuirass and the patient. The cuirass is thus used to produce counter-pressure, so that when the bladder is inflated more pressure is exerted against the upper abdomen. The tight fitting belt insures minimal rising of the cuirass as inflation takes place. In addition, two bladders of a different style were constructed. One was considerably larger than the original, was rectangular in shape, and measured 12 by 18 in. (fig. 2*F*). The second was designed similarly to water wings, with each wing about 8 in. across. (fig. 2*E*). This bladder is placed in such a way that the isthmus lies over the epigastrium and the wing-like parts extend laterally over the lower portion of each side of the chest as well as the upper abdomen. Additional studies were then undertaken to appraise the usefulness of the cuirass-like form as well as each particular type of bladder.

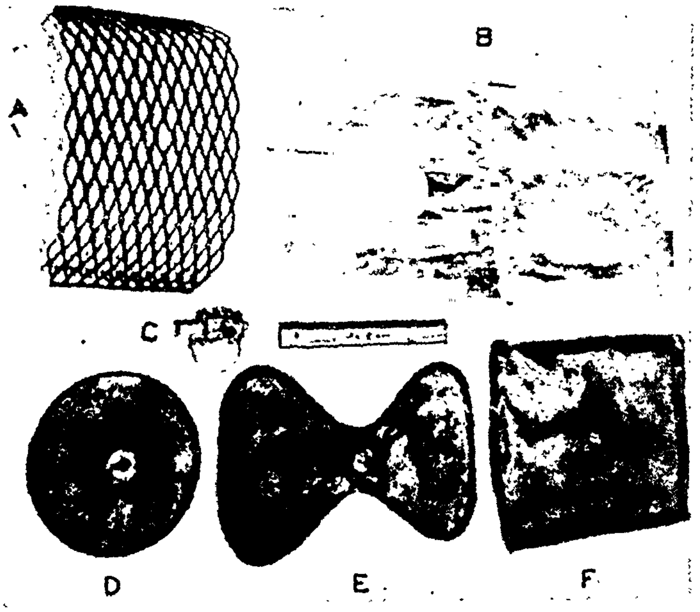

Fig. 2.—Modification of attachments for IPPB device showing *A*, molded plastic cuirass; *B*, canvas belt; *C*, Emerson valve; *D*, *E*, and *F*, inflatable abdominal bladders.

The modified apparatus with use of the small bladder was tried on 15 additional patients. The average values for ventilation at rest (10.6 liters per minute) and with use of the IPPB device alone (18.1 liters per minute) were almost identical in this group to those found in the first group studied. In contrast to the fall in ventilation which had been observed when the canvas belt was used, ventilation was maintained when the cuirass was added to the IPPB apparatus. In this group the average tidal volume was greater with use of the cuirass (1,146 cc.) than with either the IPPB apparatus alone (1,070 cc.) or at rest (662 cc). The average expiratory flow rate was 52 liters a minute compared to 48 liters a minute with use of the IPPB device alone. Actually, in 9 of 15 patients, or 60%, there was greater ventilation with use of the cuirass than with the IPPB device alone.

Similar measurements made with both the water wings and large rectangular bladders revealed values for ventilation which were intermediate. Ventilation was less than when the cuirass and small bladder were used but somewhat greater than had been observed with the unmodified canvas belt. This occurred in spite of the fact that the tidal volume was slightly higher with use of the water wings and with the large rectangular bladder. No difference was noted in the expiratory flow rate.

Subjectively there was significant approval in 5, or 33%, of the patients and a slight preference in the remainder. There were no patients who disliked using the cuirass modification. Despite the lack of objective evidence that the use of the cuirass and the IPPB device resulted in a significant improvement, in the various parameters studied, over the use of the IPPB device alone, most subjects studied felt that the cuirass and the IPPB device helped them to "breathe better." It was difficult to elucidate the exact manner in which this combination produced the feeling of improvement. There was no unanimity of opinion that the air was expired with greater ease or speed. Some patients felt that the cuirass provided support and that it felt easier to breathe with this support. Again there was no clear-cut reason as to how or why it felt easier to breathe with the support offered by the cuirass.

Comment

The treatment of chronic pulmonary emphysema is often discouraging for both the patient and the physician. Accordingly, the use of any new piece of equipment must be explored fully. The apparatus tested here has adapted two well-established methods of treatment from different eras and incorporated them into one machine. Intermittent positive-pressure breathing has been successfully used in the last decade, particularly in the treatment of respiratory acidosis. Abdominal belts, including the Gordon-Barach emphysema belt, were widely used during the 1930's. We hoped to assist the elastic recoil of the lung during expiration as well as to elevate the diaphragm and decrease the residual volume. The use of a motor-driven inflatable abdominal belt to accomplish this appears to be a logical advance.

Adamson,[2] who used a motor-driven abdominal belt in the treatment of residual respiratory paralysis after poliomyelitis, was highly enthusiastic about its ability to increase ventilation. However, the transference of a mechanical respiratory aid such as the Drinker respirator from patients with neurological disease to patients with pulmonary emphysema has not always been as uniformly successful as anticipated.

The patient with pulmonary emphysema has a relatively rigid chest wall, which is less easily moved by externally applied pressures, than the patient with only neurological disease. The parenchyma of the lung itself is markedly altered. There is a loss of elasticity and compliance. There is obstruction of the air passages due to retained secretions, bronchospasm, or mucosal hyperemia and edema which impedes the egress of air. All these factors would limit the degree to which expiration could be increased by the application of external pressure. Even so, the debilitation of the patient is frequently such that any improvement at all might well be of considerable benefit.

Combination of this primarily expiratory aiding device with an intermittent positive-pressure apparatus which is most effective as an aid to inspiration would theoretically be ideal. The positive pressure on inspiration could hyperventilate the lung as a whole and aerate hypoventilated areas. The belt could aid expiration through less obstructed air passages and reduce the residual volume, thus having a complementary action. It could also change the expiratory effort from the passive type that is usual with the IPPB device to an active phenomenon. This would be done without any increased effort on the part of the patient, and, indeed, with probably less work. The minimization of actual mechanical effort in producing hyperventilation in patients with emphysema is important. It has been shown that, when hyperventilation is achieved by purely voluntary effort, it is frequently unsuccessful in lowering the pCO_2.[3] This is the result of the greater production of carbon dioxide associated with the increased work of breathing.

This apparatus appears to have some value symptomatically. In general, there was subjective preference for use of the belt in most patients. This preference was, however, mild in many instances and its significance is hard to interpret as is frequently the case when a new method or new drug is introduced for the treatment of patients with chronic disorders. Objective measurements were not helpful, since in many cases the degree of hyperventilation was decreased when compared to that attained with use of the IPPB device alone. However, addition of the cuirass-like modification did improve this to the point that hyperventilation of equal magnitude was attained.

The obvious discrepancy between the lack of objective improvement and the subjective improvement in many patients may be explained theoretically. It is possible that the degree of mechanical work by the patient was reduced. Any decrease in the voluntary effort necessary to achieve adequate hyperventilation in these patients would result in subjective improvement. Thus, despite the absence of change in the expiratory flow rate or total ventilation, the patients thought they could breathe better.

Summary and Conclusions

Treatment with an intermittent positive-pressure breathing (IPPB) apparatus combined with an abdominal belt was favorably received by most patients who have used it. There appears to be little, if any, increase in objective measurements of improvement in this group over that normally obtained with use of the IPPB device alone. The applicability of this apparatus would thus need to be appraised on an individual basis, with particular reference to the degree of subjective improvement of the patient's condition.

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The equipment used in this study was supplied by the J. H. Emerson Company, Cambridge 40, Mass.

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"SNOWMAN" HEART

MANIFESTATION OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

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A boy with a history of cardiac disease in childhood was admitted to a hospital for evaluation of his cardiac status at the age of 16 years. Roentgenography in the frontal projection showed a "snowman" configuration of the heart, which was enlarged in the transverse diameter and had a contour suggesting right ventricular hypertrophy. The electrocardiogram suggested right atrial enlargement and right ventricular hypertrophy. Cardiac catheterization demonstrated a higher oxygen saturation in the right side of the heart than in the systemic arterial circulation. The findings were diagnostic of an anomalous connection between pulmonary and systemic veins at a supracardiac level with an atrial septal defect. The diagnosis is important because of the retardation of growth and the mortality among infants with this condition, which can now be corrected surgically.

Total anomalous pulmonary venous connection is a rare congenital anomaly, originally described by Wilson[1] in 1798. The condition generally manifests itself in early infancy and childhood and has a poor prognosis. The purpose of this paper is, first, to report an unusual case of this anomaly and, second, to stress the importance of early diagnosis, by means of the "snowman" cardiac configuration, as seen on the routine roentgenogram, particularly in view of recent surgical advances which permit successful correction of the disorder.

In patients with this anomaly, all of the pulmonary veins enter the right atrium or its tributaries. In most instances, the pulmonary veins converge at the level of the left atrium and empty into the right heart through a single anomalous vein arising from this confluence.[2] The net effect of this abnormality is the recirculation of blood in the lesser circulation, an increased work load on the right heart, and deprivation of the systemic circulation of its normal share of oxygenated blood. A classification of the levels of the pulmonary venous drainage into the right heart has been proposed by Darling and co-workers,[3] as follows. 1. Supracardiac level: a persistent left superior vena cava generally unites the common pulmonary venous trunk to the left innominate vein, which drains into the right superior vena cava and caudally into the right atrium. Direct communication to the right superior vena cava occurs less frequently. 2. Cardiac level: drainage occurs directly into the right atrium or into the coronary sinus. 3. Infracardiac level: the connection to the systemic venous circulation is by way of an anomalous vein extending below the diaphragm. 4. Combined levels: the connections to the systemic venous circulation are found at two or more levels of the right heart. In our patient the anomaly was of the supracardiac type and showed the characteristic "snowman" cardiac silhouette on roentgenographic examination.

Report of a Case

A 16-year-old boy was admitted to the Roosevelt Hospital in September, 1959, for evaluation of his cardiac status. His mother's pregnancy had been uncomplicated and the delivery, although three weeks before term, had been uneventful. He had apparently been in good health until the age of 6 months, when he became ill with pneumonia. It was at this time that a diagnosis of congenital heart disease was first made. When the patient was 1 year old, a pediatrician confirmed the diagnosis of congenital heart disease and informed the parents that there was "clubbing of the fingers" and "a hole in the heart." Otherwise, the boy apparently developed normally; he sat up at age 6 months, walked at 13 months, began speaking at 18 months.

Cyanosis, in the form of "blueness of the lips," together with shortness of breath, was first noted, according to the parents, after strenuous activity when the boy was 7 years of age. Two years later, after a complete examination which included an electrocardiogram, the parents were advised not to submit the boy to tonsillectomy. His activities, as far as sports are concerned, had been curtailed on medical counsel since he entered school. He was able to perform moderate exercise without apparent difficulty, and transient cyanosis and dyspnea occurred only after more vigorous exertion.

On the present admission, seven years later, physical examination revealed an alert, thin, poorly developed boy, who appeared much younger than his stated age. He weighed 75 lb. (34 kg.) and was 60 in. (152 cm.) tall. His blood pressure was 104/68 mm. Hg in the right arm and 106/70 mm. Hg in the left; the pulse rate was 84 and the respirations 22 per minute. There was no axillary, facial, or thoracic hair and only scanty pubic hair. The head was normocephalic, with a high and slightly arched palate. Examination of the eyes, including funduscopy, showed them to be unremarkable. The tonsils were found to be hypertrophic but not erythematous. The chest had good bilateral expan-

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sion, and there was prominent venous circulation over the superior anterior hemithorax and the left shoulder. The lungs were clear to percussion and auscultation. The heart showed the point of maximum impulse to be visible and palpable in the fifth intercostal space, 2 cm. to the left of the midclavicular line, and percussion showed it to be enlarged to the left. A harsh grade 3 systolic murmur was heard throughout the precordium, with maximum intensity, parasternally, in the third left intercostal space. Regular sinus rhythm was noted. The second pulmonic sound was louder than the second aortic sound, and a third heart sound was thought, by some observers, to be present at the apex. The liver was palpable 2 cm. below the right costal margin and was not tender. There was clubbing and cyanosis of the fingers. No other physical abnormalities were noted.

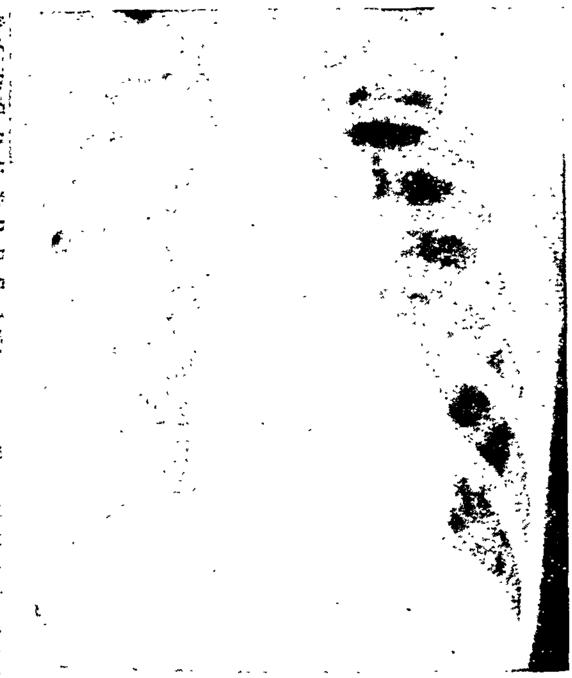

Fig. 1.—Posteroanterior chest film, showing a "snowman" cardiomediastinal configuration, considered to be pathognomonic of total anomalous pulmonary venous connection of supracardiac type.

A complete blood count showed a hemoglobin level of 17 Gm.% and a white blood cell count of 8,100 per cubic millimeter, with a normal differential count. Urinalysis showed no abnormalities; values for the blood urea nitrogen, fasting blood sugar, and serum mucoproteins were within normal limits.

Roentgenographic examination of the chest with barium in the frontal, lateral, and oblique projections revealed a poorly developed thorax, increased pulmonary vascularization, and enlargement of the heart in the transverse diameter, with the contour suggesting right ventricular hypertrophy. No other chamber enlargement was demonstrated. The most striking finding was the "snowman" configuration of the heart in the frontal projection (fig. 1).

The electrocardiogram (fig. 2) showed slightly peaked P waves, which suggested right atrial enlargement. Incomplete right bundle-branch block, right-axis deviation, as well as large R prime waves and T-wave inversions in the right precordial leads suggested right ventricular hypertrophy.

Cardiac catheterization was performed with a no. 7 catheter through the left median cubital vein to the heart. As indicated in the table, the left subclavian vein was normally saturated (76%), but an abrupt increase in saturation (97%) was noted when the catheter reached the lower portion of the right superior vena cava. The increased saturation was carried through to the pulmonary artery, where the saturation was somewhat less (88%), because of mixing with blood from the inferior vena cava. The pulmonary artery pressure was somewhat damped, but there was a small gradient across the pulmonary valve such as is often seen when a large left-to-right shunt occurs. The catheter was also passed from the right atrium to the left atrium and to the left ventricle, which indicated an atrial defect or common atrium. The reduced oxygen saturation in the femoral artery (90%) was related to a small right-to-left shunt at the atrial level. A dye curve (Evans blue, T-1824) at the level of the lower right atrium indicated a large left-to-right shunt. The right-to-left shunt indicated by the reduced arterial oxygen saturation was not shown on the dye curve, either because the shunt was of insufficient magnitude or because of the low position of the catheter in the right atrium, which permitted passage of the dye directly into the right ventricle rather than through the atrial communication.

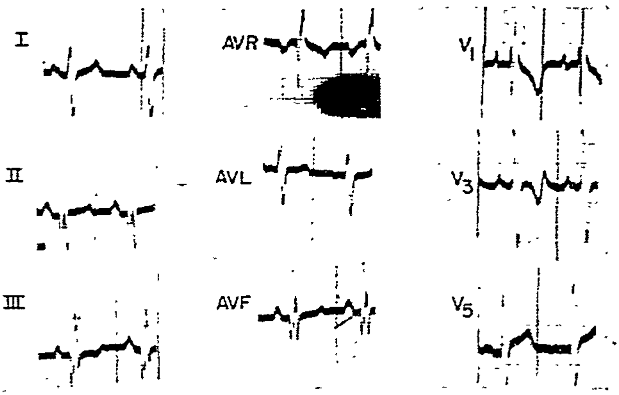

Fig. 2.—Electrocardiogram, showing right-axis deviation, incomplete right bundle-branch block, and probable right ventricular hypertrophy. Contour of peaked P waves suggests right atrial enlargement.

Data Obtained at Cardiac Catheterization

Site	O_2 Saturation, %	Pressure, Mm. Hg	
		Instantaneous	Mean
Subclavian vein	76	...	...
High superior vena cava	89	...	...
Low superior vena cava	97	...	...
Right atrium, middle	91	...	4.5
Right ventricle, middle	92	57/12	...
Main pulmonary artery	88	...	20.0+
Left atrium	89	...	5.5
Left ventricle	93	95/4	...
Femoral artery	90	...	...

A diagnosis was made of complete anomalous pulmonary venous connection via the left and right superior venae cavae and of atrial septal defect. On the patient's discharge, a recommendation for surgical correction of this deformity was made.

Comment

In an analysis of 159 cases reported in the literature up to 1958, Guntheroth and co-workers [2] found that 57% were of the supracardiac type. Of the latter group, 48% of the patients had drainage into the left superior vena cava (as in the patient reported here) and 9% into the right superior vena cava. Venous return at the cardiac level was found in 32% of the 159 patients, of whom 14% had drainage into the coronary sinus and 18% into the right atrium. Of the remaining cases, 9% were of the infracardiac type and 2% of the combined type.

It is considered by some investigators [4] that total anomalous pulmonary venous connection arises embryologically, either from a failure of communication between the atrial portion of the heart and the pulmonary portion of the splanchnic plexus or from secondary obliteration of this communication. An atrial septal defect is always associated with this anomaly if life is sustained, in most cases in the form of a midatrial septal defect or a patent foramen ovale.[5]

The clinical features presented by these patients, mainly children, are those of retarded growth, exertional dyspnea and fatigue, and little or no cyanosis. These findings were all easily discernible in our patient. Clubbing of the fingers, as well as prominence of the left side of the chest, may also be present. Cardiac enlargement of a moderate degree is seen in the form of right ventricular hypertrophy. A soft systolic murmur may be present, with maximum intensity at the left sternal border. A third heart sound has been described by some investigators; an audible hum at the base of the heart has also been variously reported. Congestive heart failure is a common sequela of this anomaly.[6]

In the case reported here, the loud parasternal systolic murmur was believed to originate in the pulmonary artery rather than as a result of the atrial communication. Experimental and clinical observation of atrial defects has demonstrated that such murmurs arise from the pulmonary artery and that the increased flow and dilatation of this vessel are important factors in the genesis of these murmurs.[7]

One of the most striking features seen in our patient was the classic “snowman” heart in the posteroanterior chest film. This feature has been variously termed “snowman” heart,[8] “figure-8” heart,[9] “mediastinal moustache,”[6c] “dumbbell-shaped” heart,[6b] and “cottage-loaf shaped” heart [10] in descriptions of the cardiac silhouette seen in the frontal projection. While the term “figure-8” heart has been used extensively in the literature since its introduction by Snellen and Albers [9] in 1952, it is our belief that “snowman” heart is a more truly descriptive term. This cardiomediastinal configuration appears only in the supracardiac type of total anomalous connection, in which drainage is accomplished by way of a left superior vena cava. The upper half, or “head,” of the “snowman” is formed by the ascent of the left superior vena cava and the prominence of the distended right superior vena cava. This configuration, when well-marked, is considered to be pathognomonic of this type of total anomalous pulmonary venous connection.[11] Of considerable importance in making the diagnosis of this abnormality is the fact that it may be detected on a routine posteroanterior roentgenogram.

There is little doubt as to the diagnosis when the “snowman” configuration is seen in full-blown form; it is when less than the classic silhouette is encountered that the following points must be considered in the differential diagnosis. In some cases, partial anomalous pulmonary venous connection has been associated with an incomplete “snowman” configuration. In addition, in a few pediatric cases, a roentgenogram taken with inadequate inspiration by the patient has produced a shadow somewhat resembling “snowman” heart, although repeat films with deep inspiration show the normal cardiomediastinal outline. Occasionally, an anterior mediastinal neoplasm may bear a slight resemblance to the “snowman” heart, but the characteristic pulmonary vascular engorgement associated with this anomaly is not present. A lateral view shows the tumor in the anterior mediastinum, and fluoroscopic examination does not demonstrate right ventricular hypertrophy. Finally, it must be remembered that certain patients with total anomalous connection of the supracardiac type do not manifest the complete “snowman” configuration. This is particularly true in infants, since it takes time to develop the typical cardiac contour.[12] However, it must be reiterated that in the presence of a well-marked roentgenographic “snowman” configuration (Figure 1), there is almost no doubt about the diagnosis.

The electrocardiogram characteristically shows right-axis deviation, right ventricular hypertrophy, and incomplete right bundle-branch block. Peaked P waves suggesting right atrial enlargement have also been reported, as well as QR complexes and inversion of the T waves in the right precordial leads.[13] Most of these characteristics are readily seen in the electrocardiogram shown in figure 2.

Cardiac catheterization demonstrates an oxygen saturation in the right side of the heart equal to, or exceeding, that of the systemic arterial saturation. This finding by itself is almost sufficient to make a diagnosis of total anomalous pulmonary venous return. In addition, pressures taken in the right heart and pulmonary artery are increased, at times to a marked degree.[14] The passage of the catheter to the left side of the heart is frequently possible, as it was in our case, thus demonstrating the presence of an atrial septal communication.

Studies made with dye dilution curves indicate that in addition to a demonstrable functional left-to-right shunt, the appearance time of the dye is longer after its injection into the right ventricle and the pulmonary artery than after its injection into the superior vena cava. This indicates that the right ventricle is functionally "upstream" to the right atrium.[14]

In our patient, the diagnosis was almost immediately apparent after inspection of the posteroanterior chest film, with its classic "snowman" configuration. Further confirmation was provided by the clinical and electrocardiographic findings, and particularly by the demonstration of higher oxygen saturation in the right side of the heart than in the systemic arterial circulation. Clinically, the boy's poor physical development was a striking feature and was a result of the diminished output of blood into the systemic circulation by the hypoplastic left ventricle. Furthermore, in contrast to normal left ventricular pressure, marked right ventricular hypertension was present, probably due to an increased flow in the pulmonary circuit and to increased work of the right heart. The occurrence of severe pneumonia when the patient was six months old confirms the observation of other investigators [15] that pneumonia is concomitant with this anomaly, in association with the increased pulmonary blood flow.

The serum mucoprotein level was measured for a possible correlation between this anomaly and Marfan's syndrome, a connective tissue disorder, in which an abnormality in the serum mucoprotein content has been observed.[16] No abnormality was found in the quantitative determination of this serum constituent in our patient.

Improved surgical techniques in recent years, together with the use of extracorporeal circulation and hypothermia, have resulted in several successful corrections of total anomalous pulmonary venous connection. Various techniques have been used, but in general they involve side-to-side anastomosis between the divided pulmonary venous trunk and the left atrium, together with closure of the interatrial communication.[17] The importance of early diagnosis and surgical correction of this anomaly must be stressed. The prognosis is poor and patients usually die in early infancy, with only a small number surviving to adult life.

Summary

Total anomalous pulmonary venous connection is a rare disorder, first observed in 1798. Some prominent clinical features are retarded growth, exertional dyspnea and fatigue, occasional cyanosis, right ventricular hypertrophy, and eventual cardiac decompensation. Early diagnosis, based chiefly on the recognition of the "snowman" cardiomediastinal configuration in the routine posteroanterior roentgenogram, is important, because, although many patients die in infancy and childhood, the development of new surgical techniques with use of extracorporeal circulation and hypothermia has permitted the successful correction of this disorder in some cases.

102-40 67th Dr., Forest Hills, L. I. (Dr. Golden).

R. A. Seitz, M.D., Cold Springs, N. Y., gave permission to use the case material.

Mrs. Rose M. Schweitzer, editor for clinical research, Mr. James Burch, medical illustrator, and Miss Marie Lopez, technician, assisted in the preparation of this report.

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J.A.M.A., July 9, 1960

IDIOPATHIC HYPERCALCEMIA OF INFANCY

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Three girls and one boy, their ages ranging from 10½ to 18 months, were brought to the physician because of retarded mental (two cases) and physical (all cases) growth. They all had in some degree the facies, here described, typical of idiopathic hypercalcemia of infancy, and determinations of the plasma calcium contents gave values ranging from 12 to 15 mg. per 100 ml. The use of a low-calcium diet, restriction of the vitamin D intake, and administration of prednisone or cortisone for three or four months reduced the plasma calcium to normal values, but only in one case was the response of the patient considered adequate as regarded physical and mental growth.

Idiopathic hypercalcemia of infancy has been reported infrequently in the United States, but there is some evidence that it may pass unrecognized because of its unfamiliarity rather than its actual rarity. On the other hand, the syndrome is relatively common elsewhere, particularly in the United Kingdom. Thus, in 1955 in one small Scottish university town,[1] this disease accounted for almost 5% of all admissions to hospitals of children between the ages of 6 and 12 months, being exceeded in frequency only by respiratory infections, feeding difficulties, and otitis media. The purpose of this report is to describe the findings in four patients with this condition, studied by us, to review the pertinent clinical and laboratory features of the disease, and to present a series of photographs of our patients and certain others previously reported in the literature. Thus it is hoped that recognition of the typical facies by the physician who may see these patients will facilitate earlier diagnosis of the condition before the full clinical picture has developed.

Report of Cases

CASE 1.—A Spanish-American boy (fig. 1, *7*) was first seen at the age of 14 months because of physical and intellectual retardation. On examination he was a moderately hypotonic infant who weighed 4.5 kg. (10 lb.) and was 65 cm. (25.6 in.) tall, both indexes being below the third percentile for caucasoid children of this age. His motor development was at the 6-month age level. A convergent concomitant strabismus was present and the facies was unusual, the jaw being small, the ears rotated forward, and the inner intercanthal distance increased. The characteristic pouting of the upper lip was not noted.

Laboratory tests on the plasma revealed the following constituent levels: calcium, 13.2 mg. per 100 ml.; phosphorus, 4.8 mg. per 100 ml.; alkaline phosphatase, 1.1 Bessey-Lowry units; cholesterol, 149 mg. per 100 ml., with cholesterol ester being 72% of the total cholesterol; and nonprotein nitrogen, 69 mg. per 100 ml. There was no evidence of hyperchloremic acidosis, the serum chloride level being 101 mEq. per liter and the carbon dioxide combining power 26.4 mM. per liter. Serum protein fractions were as follows: albumin, 3.2 Gm. per 100 ml.; alpha-1 globulin 0.29 Gm. per 100 ml.; alpha-2 globulin 0.87 Gm. per 100 ml.; beta globulin 0.91 Gm. per 100 ml.; and gamma globulin 0.82 Gm. per 100 ml. The lipoprotein electrophoresis pattern was normal. The fasting serum vitamin A level was 8 μg per 100 ml. Result of urinalysis was normal. Roentgenograms of the long bones appeared normal; however, there was an increase in density over the base of the skull and surrounding the orbits (fig. 2). The child was treated with administration of a low-calcium milk; prednisone, 5 mg. twice a day; and a vitamin D-free diet. Four months after this regimen was started the serum calcium level was 9.2 mg. per 100 ml. and that of nonprotein nitrogen 31 mg. per 100 ml. Despite the continuation of adrenocortical steroid and low-calcium milk treatment and the maintenance of a normal biochemical equilibrium, the patient's mental status was not appreciably improved.

CASE 2.—An 18-month-old girl (fig. 1, *1*) was admitted because of failure to thrive, anorexia, and irritability since the age of 4 months. On examination, she weighed 6.3 kg. (13 lb. 13 oz.) and was 70 cm. (27.6 in.) tall, both values being below the third percentile for her age. In addition she exhibited motor retardation. She was irritable and hypotonic, with the characteristic "elfin facies" of patients with idiopathic hypercalcemia. A grade 2 precordial systolic murmur was heard, but the blood pressure was normal. Two months previously the blood pressure had been reported to be 140/100

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mm. Hg and she had been treated with reserpine (Serpasil).

Laboratory tests on the plasma showed the following constituent levels: calcium, 13.8 to 15 mg. per 100 ml.; phosphorus, 3.7 to 4.1 mg. per 100 ml.; alkaline phosphatase, 9.2 Bessey-Lowry units; cholesterol, 155 mg. per 100 ml.; with ester cholesterol being 75% of the total cholesterol; chloride, 104 mEq. per liter; and carbon dioxide combining power, 21.6 mM. per liter. Result of urinalysis was normal. On roentgenographic examination of the skull, some periorbital increase in bone density was noted but the long bones appeared to be within normal limits.

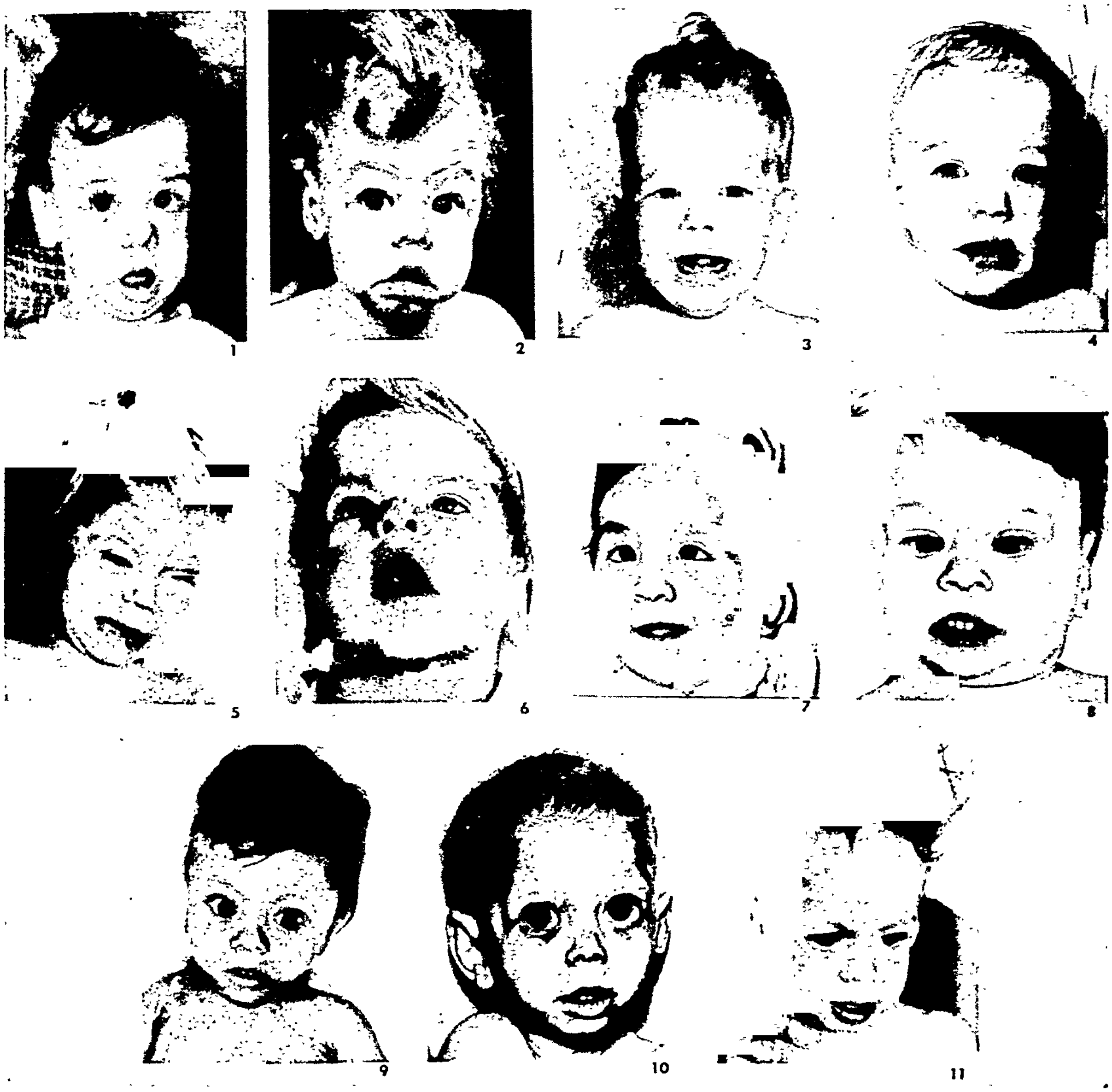

Fig. 1.—Typical facies of idiopathic hypercalcemia. *1,3,4,7,* our own patients; *2* and *6,* reprinted with permission of Dr. Bernard Schlesinger from the *British Medical Journal* (**1**:131 [Jan. 21] 1956) and *Helvetica paediatrica acta* (**7**:336 [Aug.] 1952); *5,* reprinted with permission of Dr. C. W. Daeschner from *Pediatrics* (**19**:363 [March] 1957); *8,* reprinted with permission of Dr. Michael Joseph from the *Archives of Diseases in Childhood* (**33**:389 [Oct.] 1958); *9,* reprinted with permission from Dr. W. S. Craig from the *Archives of Diseases in Childhood* (**29**:475 [Dec.] 1954); *10,* reprinted with permission from Dr. K. G. Lowe; and *11,* reprinted with permission of Dr. A. M. Bongiovanni from the *New England Journal of Medicine* (**257**:952 [Nov. 14] 1957).

Initially, she was treated with cortisone, 75 mg. daily, and a vitamin D-restricted diet. This was gradually decreased and ultimately discontinued after three months when the serum calcium and nonprotein nitrogen levels were normal. Although she showed considerable symptomatic improvement, motor and mental retardation continued.

Case 3.—A 12½-month-old girl (fig. 1, *3*) was admitted because of poor weight gain since the age of about 3 months. She weighed 6.1 kg. (13 lb. 5 oz.) and was 65 cm. (25.6 in.) tall, both measurements being below the third percentile for her age. She exhibited moderate hypotonia and had the facies of patients with idiopathic hypercalcemia but without strabismus. The rest of the physical examination was not remarkable.

Laboratory tests on the plasma showed the following constituent levels; calcium, 12.0 mg. per 100 ml. on two occasions; phosphorus, 4.0 mg. per 100 ml.; alkaline phosphatase, 2.2 Bessey-Lowry units; cholesterol, 201 mg. per 100 ml.; nonprotein nitrogen, 18 mg. per 100 ml.; alpha-2 globulin, 0.79 Gm. per 100 ml.; and gamma globulin, 1.39 Gm. per 100 ml. There was no metabolic acidosis. The fasting vitamin A level was normal (61 μg per 100 ml.), with a subnormal rise to 71 μg per 100 ml. after a test dose of 0.75 mg. per kilogram of body weight of vitamin A palmitate. Urinalyses and roentgenograms of the long bones and skull showed normal findings.

Fig. 2 (case 1).—Roentgenogram of skull in patient before treatment.

Despite the characteristic facies, she was considered to have an intermediate form of the disease hich was already showing evidence of remis- treated with a low-calcium, vitamin D-restricted diet. On subsequent examination she was noted to have normal mental development, but her physical progress was still delayed.

CASE 4.—A 10½-month-old girl (fig. 1, A) was hospitalized because of failure to thrive, anorexia, irritability, and vomiting since the age of eight months. On examination the child was noted to be pale and poorly nourished. She weighed 6.3 kg (13 lb. 13 oz.) and was 68 cm. (26.7 in.) tall, just at the third percentile for her age for height and weight. Despite the absence of hypotonia, hypertension, and cardiac murmurs, a diagnosis of idiopathic hypercalcemia was considered because th facies was characteristic of that condition. The diagnosis was confirmed when the serum calcium levels were found to be elevated on several occasions to levels between 12 and 13 mg. per 100 ml. Other laboratory data included determinations of serum nonprotein nitrogen level, 41 mg. per 100 ml.; phosphorus level, 4.6 mg. per 100 ml.; alkaline phosphatase level, 6.0 Bodansky units; and cholesterol level, 192 mg. per 100 ml. The serum proteins showed a raised alpha-2 globulin level of 0.9 Gm. per 100 ml. and a distinctly and unexpectedly low gamma globulin level of 0.3 Gm. per 100 ml. The other serum protein fractions were normal, with an albumin level of 3.8 Gm. per 100 ml., alpha-1 globulin level of 0.2 Gm. per 100 ml., and beta globuli level of 0.6 Gm. per 100 ml. Results of urinalyses were normal. Roentgenograms revealed no abnormalities.

The patient was treated for four months with prednisone, 3 to 5 mg. per day, a low-calcium diet, and restriction of vitamin D intake. On this regim the calcium and nonprotein nitrogen levels fell normal and remained so after treatment was dis continued. She was considered to have an intermediate form of idiopathic hypercalcemia with the typical facies, which responded adequately to a minimum of treatment.

Comment

The four patients herein described demonstrated varying degrees of idiopathic hypercalcemia o infancy. This condition has been divided into two varieties, a chronic, more severe form[2] and a milder, transitory variety.[3] The severe type is characterized by symptoms referable to the hypercalcemia, namely, failure to thrive, anorexia, vomiting, constipation, polyuria, and muscular hypotonia, but there may also be physical and mental retardation, a characteristic 'elfin' facies, significant but usually unexplained systolic cardiac murmurs, hypertension, osteosclerosis, and microcephaly with craniosynostosis. In patients with the mild type, the findings are generally limited to those usually associated with hypercalcemia. The characteristic facial configuration noted in many, but not all, patients with the severe cases of the disease and occasio ally found in those with the milder form, is a notable part of the syndrome. This facies is due to the presence of a combination of features[4] including a pinched, snub nose with the nostrils pointing forward, underdevelopment of the bridge of the nose and mandible, prominent epicanthal folds, a concomitant squint, a prominent loose upper lip, an open mouth which may be asymmetrical, a slack hanging lower lip, narrow temples, large ears, and a rounded, sometimes prominent forehead. The head is frequently held extended, thus making the ears appear low. This description is perhaps best illustrated by patients *1* to *4* in figure 1. The cause of the characteristic facies is unknown, although some authors have suggested that it is due to abnormal growth of the basisphenoid. However it would appear likely that not all of the facial characteristics are due to bony changes, inasmuch as some of the features appear to result from alterations in the contours of the soft tissues as well.

In the typical case of idiopathic hypercalcemia, the clinical features first appear between the 2nd and 8th months of age. The initial symptoms are not specific and may be insidious in their onset with irritability, loss of appetite, listlessness, and failure to thrive being the first changes noted by the parents.

As the name of the disease implies, the characteristic laboratory finding is an abnormal elevation of serum calcium content. This ranges between 12 and 18 mg. per 100 ml. In cases uncomplicated by renal failure due to diffuse calcium deposits throughout the kidney, the serum phosphorus and phosphatase levels are within normal limits. The urine is usually acid and may contain a moderate excess of albumin and leukocytes. The blood urea nitrogen level may be elevated and serum electrophoresis may show an elevation of the alpha-2 and gamma globulin fractions in the serum.[5]

In some patients the ratio of free to esterified cholesterol has been elevated, the beta lipoprotein–bound cholesterol level increased, and results of vitamin A absorption tests abnormal in that fasting levels were high and rose to unusually high levels after a standard loading dose. The electrophoretic mobility of serum beta lipoproteins may be altered also.[6] Associated renal acidosis has been reported on several occasions.[3a] Early in the disease roentgenograms may reveal bands of increased density at the metaphysial margins of the long bones and metacarpals, while in the later stages a variable degree of osteosclerosis of the base of the skull and orbit as well as of the vertebrae and long bones, is usually found. In addition retardation of epiphysial development may occur. In those patients who have died, diffuse calcium deposits have been found in the kidneys and other internal organs. The kidneys may also show evidence of tubular destruction, hyalinization, and fibrosis of the glomeruli.[7]

Management of these children has thus far been aimed primarily at reducing the concentration of calcium in the serum, and various forms of therapy have been tried with mixed success. These include low-calcium and vitamin D-restricted diets,[8] the administration of adrenocortical steroids,[9] and the oral use of calcium-binding agents such as ethylenediamine tetra acetate (EDTA),[1] sodium phytate,[1] and sodium sulfate[10] to lower calcium intake.

Therapy with EDTA and sodium phytate was soon discarded because of gastrointestinal symptoms in the case of the former and unconvincing efficacy in the case of the latter. In all instances vitamin D supplements should be withheld and the children given some form of a low-calcium diet; a special low-calcium formula is particularly convenient. Adrenocortical steroids are of especial value in the therapy of severe cases and when low-calcium milk and cereals are not readily available.[9] The dose of the steroids must be individualized; the optimum is the smallest which will effectively lower the concentration of serum calcium to within the normal range.

The prognosis in idiopathic hypercalcemia is variable. In many patients the severe form has been associated with a progressively downhill course, death resulting within the first five years; others have survived but were mentally retarded.[11] The milder type generally tends to remit spontaneously, with complete recovery occurring after several months. However, recent reports in the literature indicate that the division into the mild and severe forms was somewhat artificial, inasmuch as some infants with the "benign" form died of the disease[7] while others have had hypertension or cardiac murmurs.[3b] Conversely, mental retardation and the typical facies are not invariably associated with the severe form.[7] There would appear, in fact, to be a spectrum of severity rather than any clear differentiation into specific varieties.[12]

Several possibilities have been suggested as to the pathogenesis of the disease. These include abnormal sensitivity to ingested calcium in the presence of primary renal disease,[2] a response to the administration of excessive amounts of alkaline laxatives,[12] an association of separate congenital defects, vitamin D toxicity due to unusual sensitivity to small excesses of the vitamin, or an inborn error of metabolism based on some enzyme defect in lipid and calcium metabolism.[13] Despite the elevated serum calcium concentration that occurs, hyperparathyroidism probably has no role, since the level of alkaline phosphatase tends to be low in patients with hypercalcemia, and with steroid therapy the concentration of phosphorus in the serum is normal and the serum calcium level falls. Likewise, there is no evidence that dietary deficiency of linoleic and arachnidonic acids plays any part in the disease.[14]

A recent report[13a] indicates that the fundamental defect is a distortion of cholesterol metabolism whereby an excessive quantity of an abnormal antirachitic steroid is produced in the serum in association with one of the lipoprotein fractions. The relatively high calcium content of cow's milk may be an important accentuating factor, since almost all infants with hypercalcemia have been fed artificial formulas of cow's milk which have four to five times more calcium than human milk. With regard to vitamin D, on the other hand, the balance of available evidence at present suggests that daily doses of below 400 I. U. do not aggravate the condition,[9a] although hypersensitivity to the vitamin may explain its hitherto greater incidence in the United Kingdom, where intakes of vitamin D of 2,000 I. U. per day were not rare. In some patients, however, evidence of activity has continued even when they were deprived of all exogenous vitamin D.

In this report special emphasis has been laid on the facies as an important guide to idiopathic hypercalcemia of infancy, and these characteristics are illustrated by the case photographs (our own and others') in figure 1.

4200 E. Ninth St. (20) (Dr. O'Brien).

Dr. Phillip Lewis gave permission to publish details of case 4.

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CHROMOSOMAL BASIS FOR CLINICAL SYNDROMES.—Chromosomal studies on human abnormalities have so far produced a number of startling results in a very short period, namely the finding of individuals with one sex chromosome less than normal, with one extra sex chromosome and with one extra small autosome. It seems probable that other abnormalities will be discovered to be due to similar chromosomal aberrations. These need not be deviations in number but could be changes in the normal morphology of the chromosomes. Since the normal morphology is now well known an alteration in, for example, arm length or the position of the centromere in any particular chromosome might be detected by making suitable measurements. A preliminary examination of this kind on the case of epiloia failed to show any change. Long-term cell cultures have been established from small biopsies of human skin from several different individuals. From these, chromosome preparations have been made which enable detailed examination of the human karyotype. Several different human abnormalities have been studied. The finding of deviations in chromosome number in cases of Klinefelter's Syndrome, Turner's Syndrome and a patient showing both Klinefelter's Syndrome and mongolism confirm previous reports.—D. G. Harnden, M.D., A Human Skin Culture Technique Used for Cytological Examinations, *The British Journal of Experimental Pathology,* February, 1960.

RETROPERITONEAL CYSTIC LYMPHANGIOMA

Lester A. Barnett, M.D., Long Branch, N. J.

A 41-year-old man had transient pain in the right lumbar area. Three days later the pain returned with nausea and vomiting; his symptoms thereafter, with physical and laboratory findings, suggested sometimes acute appendicitis and sometimes intestinal obstruction due to a mass in the vicinity of the spleen. The explanation at laparotomy was found to be a large retroperitoneal cystic lymphangioma. It was removed despite dense adherence to the descending colon. A second operation became necessary later to relieve, by temporary colostomy, obstruction caused by an inflammatory mass in the descending colon, suggesting diverticulitis, to which portions of the ileum were adherent. No further trouble ascribable to the tumor has been observed in the three years since the second operation. This tumor is believed to be a true neoplasm, benign in nature, and only 16 previous cases are known to have been described.

The first case of retroperitoneal cystic lymphangioma was reported by Gaudier and Gorse in 1913.[1] While there have been many reports on chylous, omental, mesenteric, and perirenal cysts of lymphatic origin or composition, true retroperitoneal cystic lymphangiomas fulfilling the criteria of pathological diagnosis are relatively rare. A review of the medical literature reveals only 16 cases, and while additional cases may not have been recognized or reported, the incidence is still extremely small. I am presenting this case because of its rarity and its interesting clinical features.

Report of a Case

A 41-year-old man was first seen for "acute appendicitis" on Dec. 8, 1956. He was complaining of pain in the right lower quadrant of 12 hours' duration, nausea, and vomiting. The pain had originated in the right posterior lumbar area three days previously but had disappeared until the onset of the present illness. The pain was intermittent, and the patient had vomited three times in the 12-hour interval. There were no bowel nor urinary symptoms and no fever nor chills. Physical examination revealed a small, nodular thyroid gland, a slightly tender cystic mass in the right lower quadrant of the abdomen interpreted as a dilated cecum, a tender mass in the left subcostal region suggesting splenomegaly, and a slight nodulation of the prostate gland. The initial clinical impression was reported as "intermittent, partial obstruction of the splenic flexure of the colon due to extrinsic pressure from a left subcostal mass, probably splenic in origin," and the patient was referred to his family physician for further study, a surgical emergency having been ruled out.

He was admitted to Monmouth Medical Center on Dec. 10, 1956, by his personal physician for further study, his symptoms having abated. It was learned that at 8 years of age the patient had suffered "swollen glands" of the left side of his neck which were treated by "operation" followed by "x-ray treatments," and that the next year his tonsils and adenoids had been removed. He had suffered a skull fracture at 9 years of age and had "yellow jaundice" at 11 years of age. When he was 34 years of age he had a bilateral inguinal herniorrhaphy, and in May, 1955, he was admitted to the Monmouth Medical Center for progressive duodenal ulcer symptoms. An upper gastrointestinal roentgenographic study at that time revealed an ulcer crater in the duodenal bulb area, but no other pathology was mentioned. His symptoms rapidly disappeared under medical treatment, with no further abdominal complaints until the present illness.

On admission a complete physical examination failed to uncover additional abnormalities other than the nodular thyroid, the mass in the left upper abdominal quadrant, and the slight prostatic nodulation; the mass in the right lower quadrant had disappeared. On admission his pulse rate was 84 per minute, respiration rate 20 per minute, and blood pressure 110/60 mm. Hg. The laboratory data were as follows: a hemogram showed 5,100,000 red blood cells per cubic millimeter, 15.5 Gm. per 100 cc. of hemoglobin, 14,800 leukocytes per cubic millimeter, of which 66% were segmented neutrophils, 3% band forms, 28% lymphocytes, and 3% monocytes, with an adequate number of platelets. The sedimentation rate was 27 mm. in one hour and the prothrombin time was normal. The glucose concentration was 90 mg.%, blood urea nitrogen level 11 mg.%, bilirubin 0.8 mg.%, thymol turbidity 2.8 units, cholesterol level 215 mg.%, cholesterol ester fraction 63%, alkaline phosphatase level 3.5 Bodansky units per 100 cc., acid phosphatase 0.5 units per 100 cc., bromsulphalein retention (45 min.) 3.3%, protein level 6.1 Gm.%, albumin 4.8 Gm.%, globulin 1.3 Gm.%, and albumin-globulin (A/G) ratio 3.7. The urine was normal. Results of biopsies of the gingiva and of the right biceps muscle revealed no pathology. A flat plate of the abdomen (fig. 1) showed the large mass in the left hypochondrium to be suggestive of splenic enlargement. An upper gastrointestinal series (fig. 2) revealed displacement of the third portion of the duodenum laterally and downward, and displacement of the upper jejunum over the upper pole of the

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From the Department of Surgery, Monmouth Medical Center.

mass; at this time the mass was considered to be separate from the spleen. An intravenous pyelogram (fig. 3) demonstrated slight displacement of the left ureter indicating a retroperitoneal location of the mass. This was further confirmed by barium enema study of the colon, which revealed the descending colon surrounding and anterior to the tumor. A chest roentgenogram was normal. Because of the Christmas holiday the patient was discharged on Dec. 21, 1956.

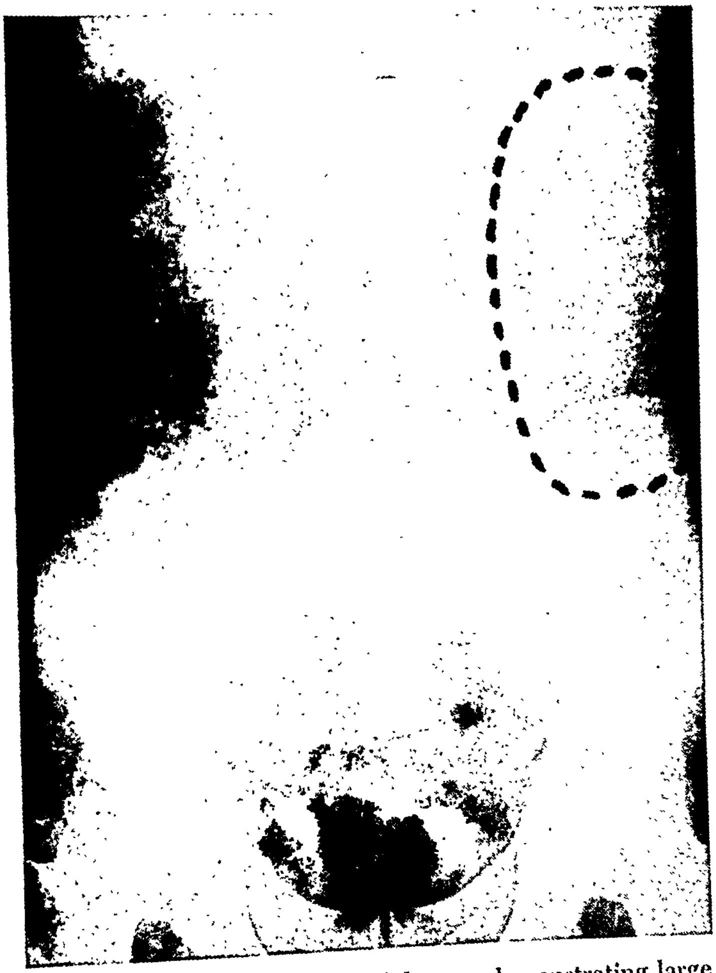

Fig. 1.—Initial scout film of abdomen, demonstrating large abdominal mass.

The patient was readmitted to the Monmouth Medical Center on Dec. 27, 1956, and operated on the next day. Surgical exploration was carried out through an upper left paramedian incision exposing the large retroperitoneal cystic mass. The descending colon was tightly stretched over the anterior surface and was densely adherent to it. The upper pole of the cyst extended to the pelvis of the left kidney and over the tail of the pancreas; it descended downward along the left lateral gutter, beneath the descending colon, into the iliac fossa. The spleen was normal in size. The esophageal hiatus, stomach, pylorus, duodenum, liver, pancreas, and gallbladder were normal on examination. The prostate could not be palpated, because rectosigmoid adhesions filled the true pelvis and prevented proper evaluation of the rectal pouch. A few diverticula were seen in the sigmoid area, but the remainder of the colon and appendix were not remarkable. The cystic mass was exposed by cutting the lateral peritoneal reflection of the descending colon and peeling the bowel medially off the anterior surface of the cyst; because of dense adherence between these structures, this process was tedious but was believed to have been accomplished without injury to the intestinal continuity. The remainder of the dissection was relatively simple, since the mass did not appear to be adherent to the other viscera in the left side of the abdomen. The colon was restored to its normal position in the left lateral gutter by reapproximating the peritoneal reflection, and the abdomen was closed without insertion of drains.

The pathologist described the specimen (fig. 4) as a roughly reniform cystic structure which measured in its contracted state 20 by 12 by 7.5 cm in its greatest over-all dimensions. It displayed a thin, semitranslucent fibrous capsule, which wa covered by occasional hemorrhagic shreds of fibrou tissue and contained colorless watery fluid. Th inner surface was smooth and glistening; a sma narrow band of tissue, gray and semitranslucent, was observed across the cavity. The microscopic

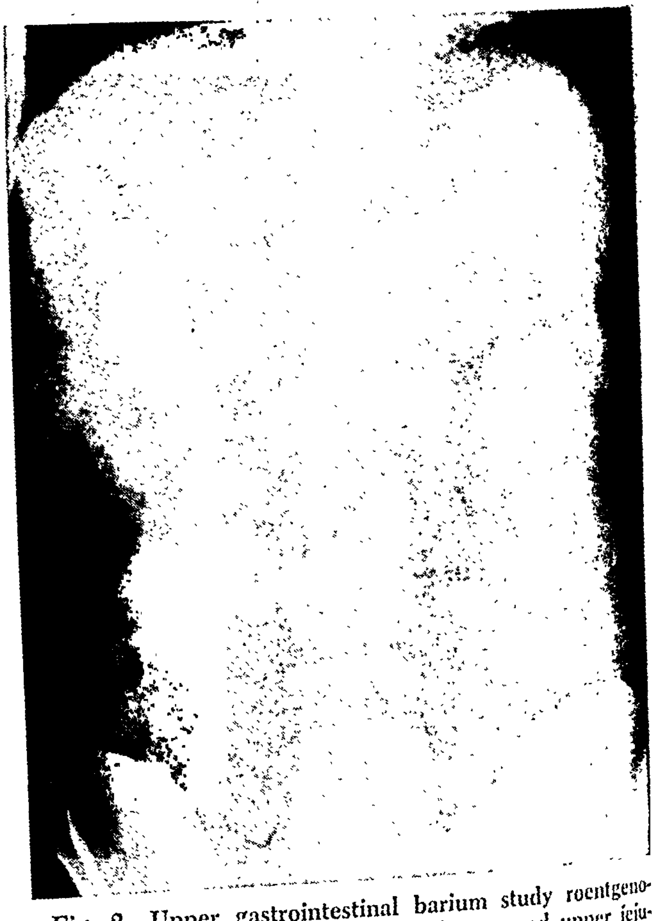

Fig. 2.—Upper gastrointestinal barium study roentgenogram, showing displacement of duodenum and upper jejunum by mass.

examination of sections of the cyst wall (fig. 5) showed a compressed endothelium with collagenized connective tissue subjacent. Aggregates of lymphoid follicles and lymphocytes were diffusely scattered, in varying degrees. Occasional inflammatory cells and areas of injected blood vessels were also noted. The histogenesis of this anomalous cystic tumor suggested derivation from the primitive blood and lymphatic vessels comparable to the cystic hygroma of the neck in children. The pathologist's diagnosis was cystic lymphangioma, retroperitoneal, benign.

With the exception of a bout of emesis on the fourth postoperative day, the patient's convalescence was uneventful and he was discharged one week from the day of operation.

On Jan. 16, 1957, 19 days postoperatively, the patient was readmitted to the Monmouth Medical Center for vomiting of 12 hours' duration, with colicky abdominal pain since the onset of vomiting. He had had no bowel movements for five days previously, although some flatus had been expelled. Physical examination revealed few positive findings since the patient appeared well and the abdomen was soft, only slightly distended, and free of masses, tenderness, and tympany. The incision was well healed and presented neither induration nor tenderness. Results of rectal examination were negative. His temperature was 37.0 C (98.6 F) orally and the hemogram showed 23,200 leukocytes per cubic millimeter, of which 83% were segmented neutrophils, 5% band forms, 11% lymphocytes, and 1% monocytes. A Miller-Abbott tube was passed and fluids given parenterally. A two-way abdominal roentgenogram demonstrated a few loops of small and large bowel with fluid levels. The next morning a barium-enema roentgenogram of the colon (fig. 6) revealed a constricting lesion measuring 3 cm. in the middle portion of the descending colon, at the level of previous operation. Decompression was accomplished to the level of the middle of the ileum while maintaining fluid and electrolyte balance during the next three days, but due to failure of the process to completely resolve an operation was performed. On Jan. 20, 1957, the descending colon was approached through a transverse left lumbar incision revealing the middle of the descending colon to be involved by a smooth, hard, inflammatory mass about 10 cm. in length, with normal colon distal and fresh adhesions of the splenic flexure proximal; two segments of distal ileum were loosely adherent to the inflammatory mass but presented no obstructive elements and separated easily by a light sweep of the examining finger. Scrutiny revealed neither evidence of leakage, abscess formation, nor loculation in the surrounding intestines and I believed that this process represented either intestinal leakage from a fine perforation which occurred during the original dissection or acute diverticulitis, which the lesion so typically resembled. To defunctionalize the involved area, a proximal transverse colon-loop colostomy was brought out of the right subcostal region through a small transverse pararectal incision and the exploratory incision was closed. The colostomy was opened 24 hours later and functioned well 48 hours postoperatively, the Miller-Abbott tube having been left in the lower ileum for additional decompression and "splinting" of the loops of released ileum. A second barium enema roentgenographic study on the 10th postoperative day (fig. 7) showed considerable regression of the narrowing, with flexibility of the segment. The patient was discharged on Feb. 4, 1957.

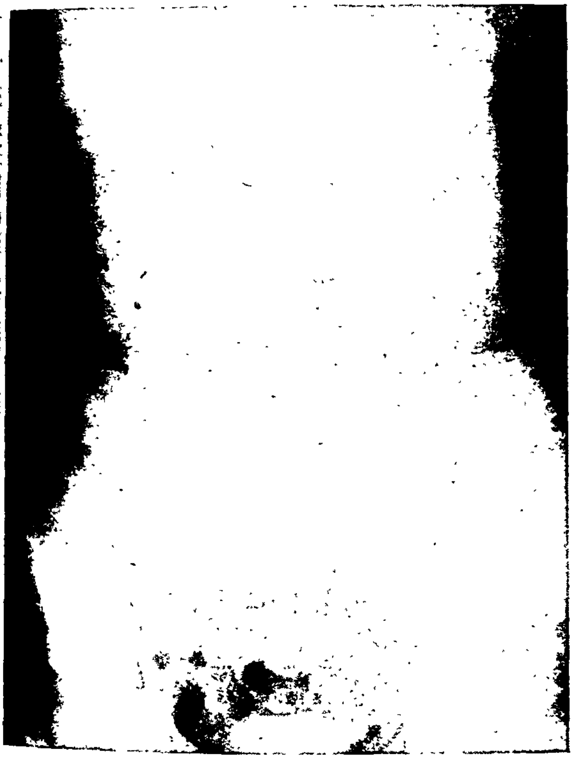

Fig. 3.—Intravenous pyelogram showing medial displacement of left ureter suggesting retroperitoneal location of mass.

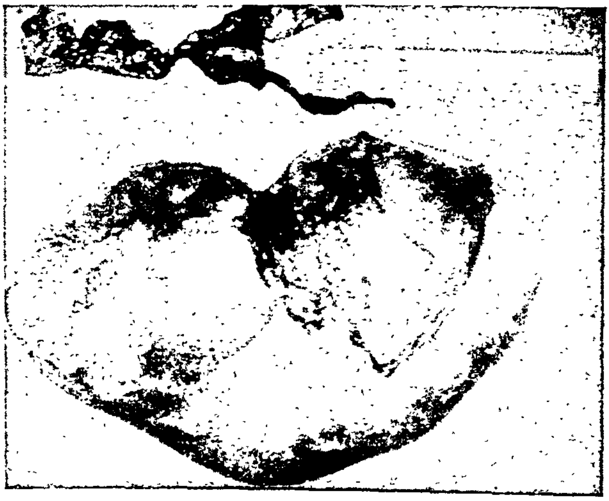

Fig. 4.—Gross appearance of retroperitoneal cystic lymphangioma.

Five weeks later, on March 12, 1957, another roentgenographic study of the colon revealed it to be completely normal, including the mucosal pattern, but with several diverticula in the sigmoid segment. The patient was admitted to the Monmouth Medical Center for the fourth time on March 19, 1957. Intestinal antisepsis was instituted, and the colostomy was closed with some difficulty because of fixation by adhesions and the close proximity to the costal margin. The patient was discharged March 29, 1957, on the 10th postoperative day.

The further history of this patient's course is interesting although unrelated to the retroperitoneal cystic lymphangioma which had given him no more trouble. On Oct. 3, 1957, at the Monmouth Medical Center, a total thyroidectomy with a left-sided modified dissection of the neck for follicular carcinoma of the thyroid was performed, at which time an incisional hernia of the colostomy site was repaired. The patient then moved to the Chicago area where he was referred to another surgeon for further study. He continued to receive thyroid therapy. On April 17, 1958, the surgeon completed a left-sided radical dissection of the neck, followed seven months later, on Nov. 14, 1958, by one on the right. At the time of this writing the patient is well, with no evidence of recurrence, and working at his usual occupation.

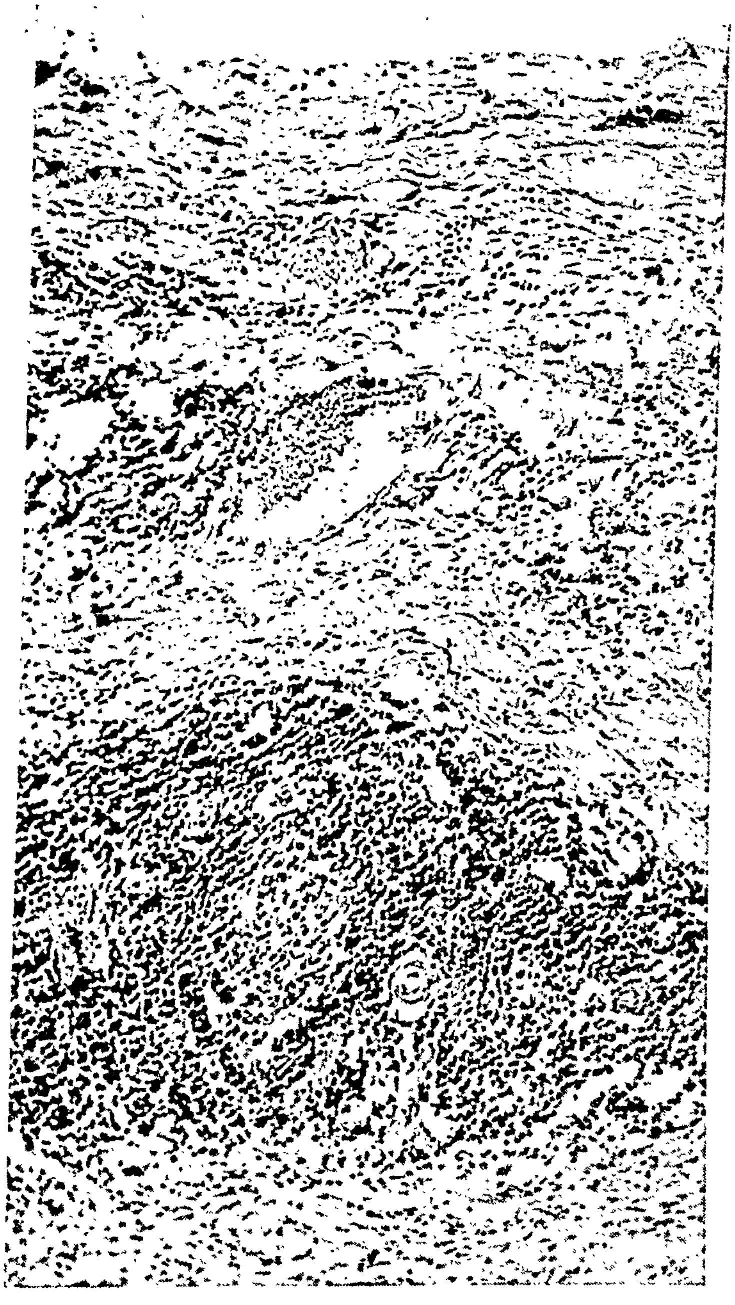

Fig. 5.—Photomicrograph, clearly demonstrating lymphocytic structures and spaces (× 150).

Review of Literature.—The rarity of retroperitoneal cystic lymphangioma is best illustrated by a brief review of the medical literature. As previously mentioned, while extensive series of abdominal, mesenteric, omental, and retroperitoneal cysts have been reported [2] few can be classified as unattached retroperitoneal cystic lymphangiomas. The reports of Gobell [2b] in 1901, Magoun [2c] in 1919, and Schmid [2e] in 1923 totaled 471 cases of retroperitoneal tumors, 12 of which were cystic in nature, but no instance of a cystic lymphangioma was reported. Gaudier and Gorse [1] in 1913 carefully surveyed the literature and then reported their patient as the first case of retroperitoneal cystic lymphangioma. Single cases were then reported by Westman [3] in 1925, McFadden [4] in 1931, Burhaneddin [5] in 1931, Kretschmer and Hibbs [6] in 1934, Gertser [6a] and Ingraham and Nelson [7] in 1939, Lingenfelter and Howard [7a] in 1951, and Hsü and Meng [8] in 1955. In 1957, Harrow,[9] reporting a case, stated that a thorough review of the English literature yielded only 14 cases that fitted the criteria for the lymphatic variety of retroperitoneal cysts; his added case and that of Hsü and Meng brought the total to 16. I offer this as the 17th recorded case.

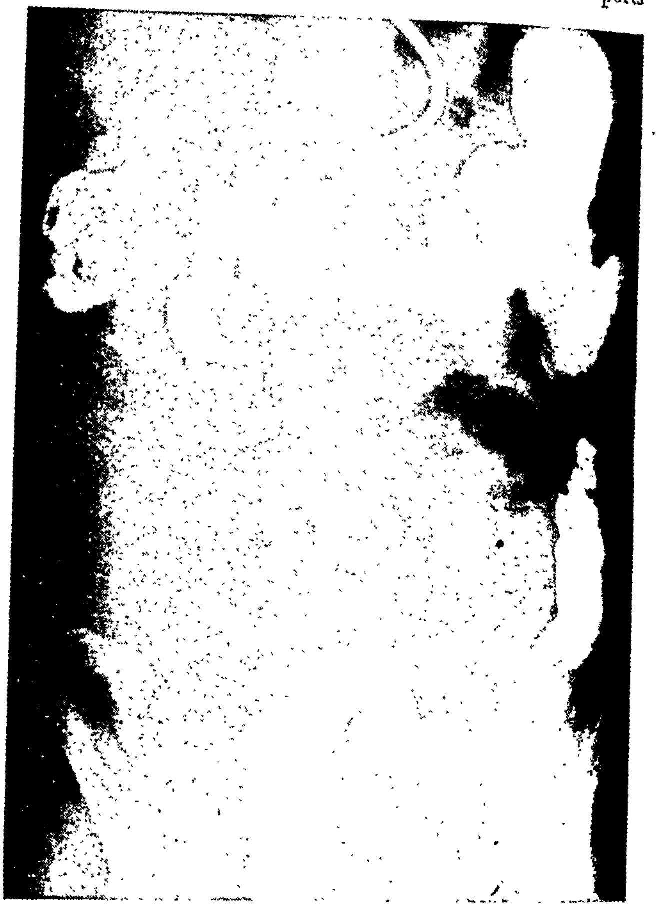

Fig. 6.—Barium enema colon roentgenogram taken 20 days postoperatively. Constricting lesion is seen in middle portion of descending colon.

Pathology

In reviewing all the cases of cystic tumors of the abdomen seen at the Mayo Clinic from 1911 to 1947 inclusive, Beahrs and colleagues [2a] suggested classification into the following four groups: (1) embryonic and developmental cysts, (2) traumatic or acquired cysts, (3) neoplastic cysts, and (4) infective and degenerative cysts. They placed the true lymphangiomas in the group of "benign neoplasms." Ewing[10] had previously stated that retroperitoneal lymphangioma occurs in children and adults as a multilocular cavernous and cystic tumor originating along the spinal column and ramifying into the pelvis behind the kidney or colon, upward to the liver and the spleen and into the omentum. He believed that the exact origin of these tumors had not been demonstrated and that their neoplastic nature seemed assured, since the walls contain cellular connective tissue, often much smooth muscle and lymph follicles. Brandsburg enumerated the following four theories of origin: (1) the retention theory, which explains lymphangioma on the grounds of mechanical pressure, (2) the theory of a disturbance of the secretory function of the endothelium of the vessels, causing hyperproliferation of the lymph, or a disturbance of the permeability of the endothelium, (3) the inflammatory theory, and (4) the embryonal theory. He favored the last, explaining the lymphangioma on the grounds of a defect in the embryonal organization of the lymphatic system, small segments of tissue retaining their embryonal characteristics.

7.—Roentgenogram taken 10 days after exploration of descending colon. Loop colostomy is seen in right upper quadrant.

Few textbooks on pathology mention retroperitoneal cystic lymphangioma. Ewing[10] included in the general class of lymphangioma a variety of slowly growing congenital single or multiple tumors of the skin, subcutaneous tissues, and deep areolar structures and muscles of the neck, axilla, trunk, lip, tongue, eye, and orbit. He believed that the general clinical features were a good indication of classifying the lymphangiomas, but most investigators would include only those showing a congenital origin and a progressive course, with an absence of traumatic and inflammatory factors. Kaufman, quoted in two excellent reports,[11] followed Wegner's original description of lymphangiomas, dividing them into (1) simple lymphangiomas, usually situated superficially in the skin, (2) cavernous lymphangiomas, found chiefly in macroglossia, macrocheilia, and more rarely in other parts of the face and skin, and (3) cystic lymphangiomas, consisting of cysts, simple or divided, lined with endothelium, the contents of which are clear, serous, milky or chocolate-colored fluids which may contain cholesterin and detritus. These tumors appear chiefly in the neck, breast, axilla, lower sacral region, abdomen, thighs, and inguinal regions. When located in the mesentery they often contain chyle, in which case they are called chylangiomas or "chylous cysts."

An attempt has been made[9] to establish identifying microscopic elements to differentiate cystic lymphangiomas from cysts of other types. 1. The lining of the cyst should be endothelial or absent and must not be cuboidal or columnar epithelium. 2. Small lymphatic spaces should be found in the wall. 3. Lymphoid tissue should be fairly abundant in the wall as diffuse collections of lymphocytes or in configurations resembling lymph nodes. 4. Foam cells should contain lipids existing in varying degrees.

Diagnosis and Treatment

There are no clinical features which serve to differentiate retroperitoneal lymphangiomas from other retroperitoneal masses. Like most retroperitoneal growths they remain silent until pressure symptoms occur or the mass is visible or palpable. Perhaps the fluctuant sensation of a cyst imparted to the examiner's fingers may differentiate it from a solid tumor but not from cysts of other types. Pressure symptoms depend largely on the location of the cystic mass, and in 40% of the cases they consist of partial or intermittent intestinal obstruction from pressure on the bowel, particularly with mesenteric cysts.[12] This produces colicky pain, nausea, vomiting, and hyperperistalsis which occur in intermittent attacks, as was so well illustrated by my patient. At times the cyst is freely movable and occasionally it is fixed and tender.

Roentgenograms may be helpful in localization by displacement of surrounding visera. A plain abdominal scout film is frequently instructive. Pyelography and barium study of the gastrointestinal tract are frequently of help in localizing the cyst and differentiating the mass from other lesions, such as renal tumor or perinephritic abscess, pancreatic cysts, or ascites. It is doubtful if retroperitoneal air insufflation studies are necessary. Further differentiation from reduplication of the intestinal tract, traumatic abdominal cyst, cystic degeneration of lymph nodes due to tuberculosis, metastatic malignancies, especially from the testes, parasitic cysts, aneurysms, and dermoid cysts can only be made during exploratory laparotomy.[2f]

The preferred treatment is complete excision of the cyst without rupture. When uncomplicated by perforation, hemorrhage, inflammation, or torsion, dissection is usually not difficult if painstaking technique is used. The chief problem lies in the dissection from the mesenterics and intestine when the cyst is densely adherent to these structures. While in previously reported cases this has occasionally required resection of portions of the intestine, in our case it probably accounted for the acute inflammatory process necessitating three additional surgical procedures. A preoperative "bowel prep" is a wise precaution should accidental injury occur or a resection be elected.

It is conceivable that under certain circumstances it would be safer to leave a small portion of the cyst wall attached to an important structure where the risk of dissection would be overwhelming, assuming that the benign nature of the lesion has been definitely ascertained. Aspiration or incision and drainage have no therapeutic place except to facilitate removal of the benign lesion. Marsupialization can be used with success[2a] when the situation contraindicates excision without rupture.

Comment

Large visible or palpable abdominal masses continue to tax the physician's diagnostic acumen. The differential diagnosis encompasses many considerations from the common ascitic collections, abscesses, and neoplasms to the less common retroperitoneal masses. The retroperitoneal cysts fall into the latter group and frequently are diagnosed only at exploratory laparotomy, although their presence is suspected after extensive laboratory and roentgenographic studies. The retroperitoneal cystic lymphangioma is a rare finding and few cases have been reported in the medical literature.

The retroperitoneal cystic lymphangioma is believed to be a true neoplasm by most investigators, and the diagnostic pathological criteria are fairly well established. Because a malignant form of this cyst has not yet been reported, these neoplasms are considered to be benign and can be surgically treated by simple excision.

This is the 17th retroperitoneal cystic lymphangioma reported in the literature and differs from the previously documented cases in its location posteriorly to the descending colon, the presenting symptom-complex of an "acute abdomen," and the complicating postoperative course. It is difficult to ascertain whether the obstructing inflammatory lesion in the colon at the site of cyst excision was diverticulitis excited by the operative procedure or a minute perforation incurred during separation of the adherent cyst from the colon. Acute diverticulitis after abdominal surgery is not uncommon even when the operative procedure was not in the region of the postoperative diverticulitis, and the presence of diverticulosis in this patient, together with the typical appearance of diverticulitis in the obstructing segment of colon, lends support to that possibility.

Summary

True retroperitoneal cystic lymphangioma is a rare lesion which cannot be detected until it causes displacement of surrounding viscera or can be palpated abdominally. Preoperative diagnosis cannot be made with consistent accuracy.

Operation with complete excision without rupture is the procedure of choice. The surgeon may depend on the benign nature of this neoplasm, since no cases of malignant retroperitoneal cystic lymphangiomas have been reported in the medical literature.

This is the 17th case of retroperitoneal cystic lymphangioma reported in the literature.

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GASTRIC LESIONS, INCLUDING EXFOLIATIVE CYTOLOGY

A DIAGNOSTIC APPROACH

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and
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All clinical and laboratory means available were used to study 300 consecutive patients with suspected gastric malignancy. The cases were evaluated by means of gastric analysis (found to be 63% accurate), roentgenography (92.7% accurate), gastroscopy (95.3% accurate) and gastric cytology (97.7% accurate). The accuracy of cytological studies giving negative results was 99.3%, and that of studies giving positive results was 72.2% (of cancer patients). Exfoliative cytological study proved to be the most accurate individual test used and ranks second only to direct biopsy. However, collective evaluation of all methods of study produced a greater accuracy than did any one test. No method of treatment can, at the present time, offer much to patients who have far-advanced cancer. The over-all diagnostic approach with use of collective evaluation will result in the detection of earlier lesions for surgery and allow earlier institution of medical management for benign lesions.

The early diagnosis of gastric cancer is, at the present time, the only feasible means of improving survival rates. Raskin and others[1] have pointed out that critical evaluation of exfoliative cytology indicates that, when properly used, this diagnostic method ranks second only to direct biopsy in accuracy and reliability in the diagnosis. Evaluation of a series of 300 cases supports this view; however, greater accuracy can be obtained by use of all ancillary methods of diagnosis and evaluating each case individually. This study relied on cytological examination to assist us in evaluating individual problems, but even this highly accurate method of diagnosis is not infallible.

Statistics

Three hundred consecutive cases of suspected gastric malignancy were evaluated with use of gastric analysis, roentgenograms, gastroscopy, and gastric cytology. The relative accuracy of the accepted methods of distinguishing malignant from benign disease of the stomach was as follows: gastric analysis, 63%; roentgenology, 92.7%; gastroscopy, 95.3%; and cytology, 97.7%. The accuracy of cytological studies giving negative results was 99.3% (of 282 patients with benign disease), and the accuracy of studies giving positive results was 72.2% (of cancer patients).

False-Negative Results.—In the series of 300 patients who had upper gastrointestinal symptoms, 282 (94.0%) had benign disease. Of a total of 18 (6.0%) cases of proved gastric cancer, 5 (27.8%) were recorded as giving negative results of cytological studies. Three of these five occurred early in our series, and, in retrospect and as we have gained experience, we would call the smears unsatisfactory and recommend repeat studies. Of the two remaining cases in which a false-negative result occurred, one patient manifested an obstructing, pyloric, ulcerating, and infiltrative carcinoma which, on histological study, did not reveal any neoplastic cells at the surface of the ulcer. We cannot explain the remaining false-negative result. Repeated tests were done, and results were reported as negative. At surgery, the patient was found to have a large, infiltrative, ulcerating mass in the body of the stomach.

False-Positive Results.—Of the 300 patients studied because of upper gastrointestinal pain, there were 2 (0.7%) for whom a false-positive gastric cytological specimen was reported. Gastroscopy was performed on both patients. They were subsequently studied for over a year, and it has been proved to our satisfaction that they do not have any malignant growth in the stomach. In one instance, the patient was suffering from pronounced hypertrophic gastritis; this was also proved true in the second case, although the condition was not so severe.

In this series there were 66 cases of benign gastric ulcers. There was 1 case reported as malignant ulcer and 13 cases reported as frank carcinoma with some ulceration. Twenty-four of the 66 benign ulcers revealed hypochlorhydria. Of the 66 benign ulcers, 18 were submitted to surgical treatment. In all instances, they were proved to be benign. All

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of the malignancies were proved by surgical exploration or autopsy. There were 48 gastric ulcers handled on a medical regimen that were diagnosed as benign on the bases of complete healing and failure to recur. In most instances, these were checked by gastroscopy and by x-ray evidence of healing; at the time of this writing this group of patients was under surveillance to be sure that there had been no instances of recurrence. In three patients the roentgenograms were suggestive of filling defects in the greater curvature of the stomach; these proved to be hypertrophied gastric mucosa in every instance. Two such patients were brought to surgery where the biopsy proved the correctness of the cytological diagnosis.

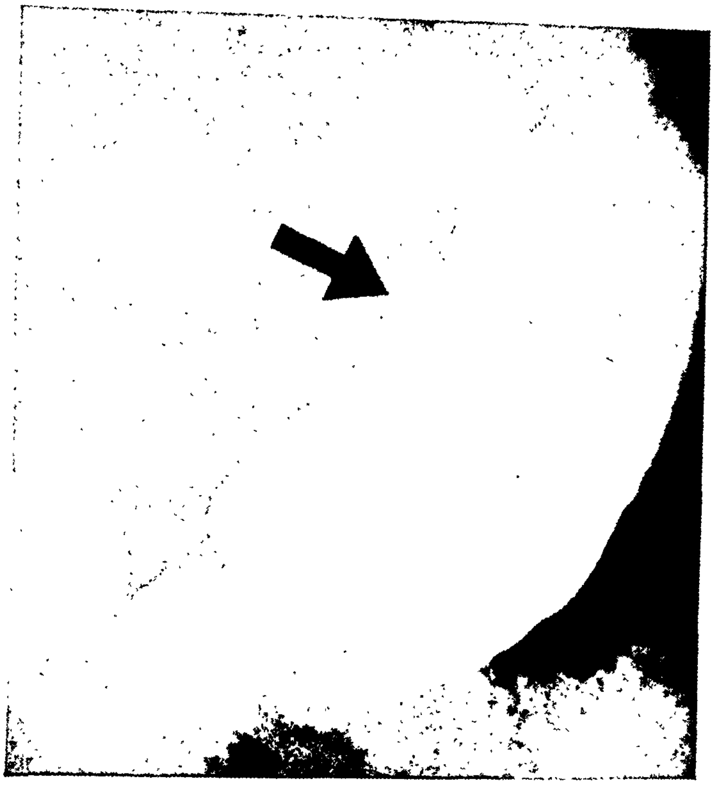

Fig. 1 (case 1).—Roentgenogram interpreted as showing gastric ulcer, equivocal as to malignancy, cytologically positive.

Epigastric pain was the predominant symptom in this series of patients; in fact, it was four times more common than any other symptom, both subjective and objective. Next in order was indigestion, then nausea and vomiting, weight loss, hematemesis, and melena. Symptoms of lesser importance included weakness, dysphagia, shortness of breath, diarrhea, and palpitation. Two patients were asymptomatic, but they were subjected to the study on the basis of a yearly examination.

Report of Cases

Case 1.—A 54-year-old man was admitted to the hospital in January, 1956, complaining of recurrent distress in the upper part of the abdomen, including fullness, bloating, and pain not related to meals, particularly for the previous three months. There had been an associated loss of weight of 10 lb. (4.5 kg.) during this time. Physical examination showed a thin man weighing 148 lb. (67 kg.), who had epigastric tenderness when deep palpat was performed. Laboratory studies revealed a r blood count of 3,800,000 per cubic millime and a hematocrit value of 34 vol.%. Gastric analy revealed a histamine achlorhydria, and the roe genograms (fig. 1) showed gastric ulcer, thought be benign, on the lesser curvature at the juncti of the middle and upper third of the stomach. G troscopy confirmed this opinion. Cytological stud gave positive results. Diagnosis of a maligna ulcer was proved at surgery.

Case 2.—A 71-year-old man was admitted to t hospital in January, 1957, complaining of gas in t upper part of the abdomen and vomiting of fo weeks duration. He had also noticed some difficul in swallowing for the same period of time and h lost 17 lb. (8 kg.). He stated that he had been good health until these difficulties had begu except for mild diabetes mellitus of 30 years dur tion. He had had a series of tests on the upper pa of the gastrointestinal tract on Dec. 6, 1956, ma by his local physician in a nearby community, an he was told that these tests gave negative resul but that he probably had an ulcer. His sympton persisted; he consulted us on Jan. 4, 1957, a was hospitalized at Hermann Hospital. Physi examination was not remarkable for a 71-year-c man except for definite evidence of being und weight. The abdominal examination gave negati results.

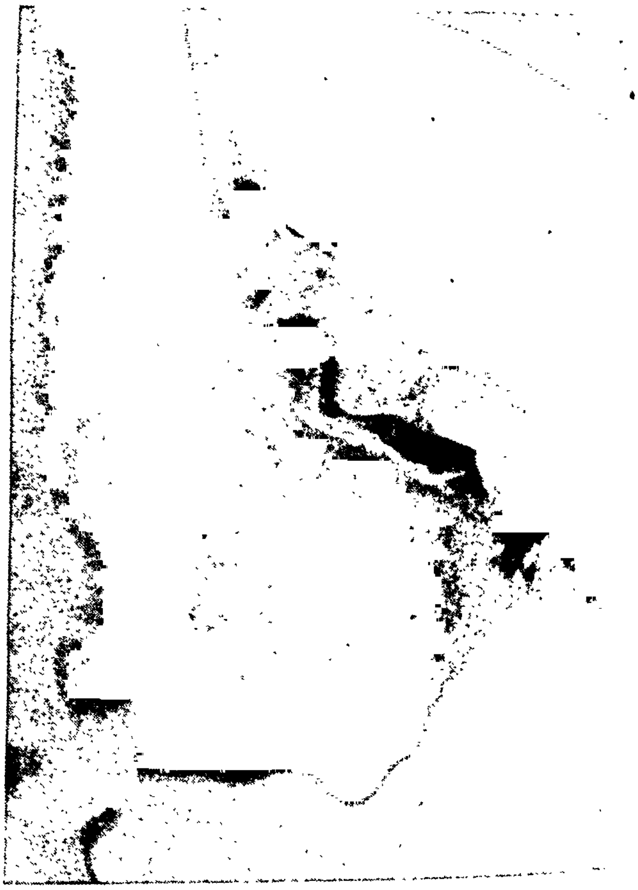

Fig. 2 (case 2).—Roentgenogram interpreted as showin filling defect in the fundus and cardia of the stomach, definite as to malignancy, cytologically positive.

Laboratory studies revealed a red blood count of 3,400,000 per cubic millimeter and a hemoglobin level of 8.9 Gm. per 100 cc. A repeat series of gastrointestinal tests (fig. 2) revealed a definite deformity of the mucosal pattern in the fundus and cardia of the stomach, which was equivocal from a radiographic standpoint. Esophagoscopy was performed, and results were negative. Gastroscopy was then performed; we were unable to distend the fundus of the stomach normally, and visualization was not adequate for definition, but due to the inability to distend the stomach we felt that we were dealing with a constricting lesion. After the gastroscope was withdrawn, its rubber tip was used to make a Papanicolaou smear, which gave positive results, as did a saline lavage. At surgery, a fundic carcinoma was found.

Case 3.—A 48-year-old woman had a history of recurrent pain in the upper part of the abdomen, nausea, vomiting, and loss of weight of one-year duration. There had been an associated 10-lb. loss of weight during this illness. The patient stated that she had had recurrent stomach trouble all her life. Physical examination gave negative results except for tenderness in the upper part of the abdomen in the thin and chronically ill woman.

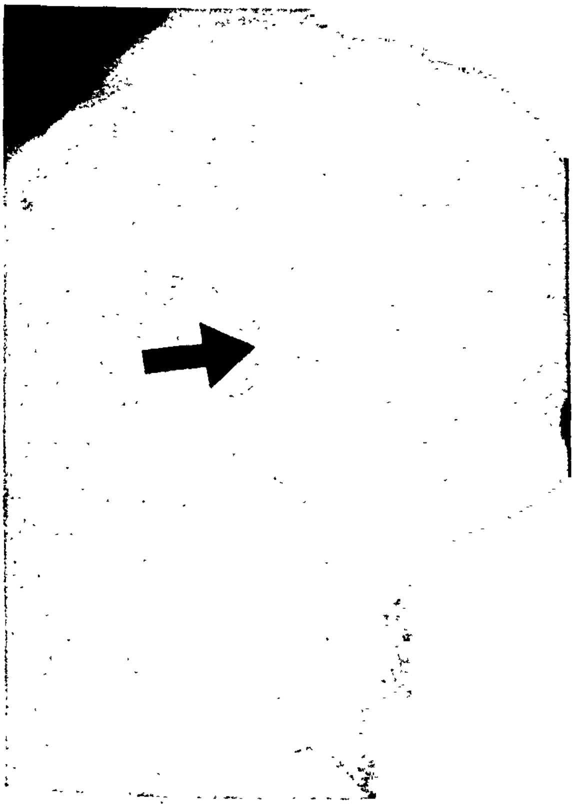

Fig. 3 (case 3).—Roentgenogram interpreted as showing malignant gastric ulcer, cytologically negative.

Laboratory studies revealed a normal red blood cell count and hematocrit value. Gastric analysis revealed an achlorhydria on a fasting specimen and after histamine stimulation. On two occasions, a series of tests on the upper part of the gastrointestinal tract (fig. 3) revealed a lesser curvature ulcer at the junction of the upper middle third of the stomach, which was felt to be a malignant ulcer. Gastroscopy was performed on two occasions, but the vision was poor due to marked distortion of the lesser curvature of the stomach and inability to completely distend the stomach. The gastroscopists thought that, although the base of the ulcer could not be visualized due to the marked distortion of the normal contours of the stomach, we were dealing with a malignant ulcer. Exfoliative cytology was carried out and gave negative results for malignancy. The patient was operated on, and a large, benign gastric ulcer was found which revealed evidence of subacute perforation; this indicated why the ulcer had not reduced in size after a medical program of three weeks duration.

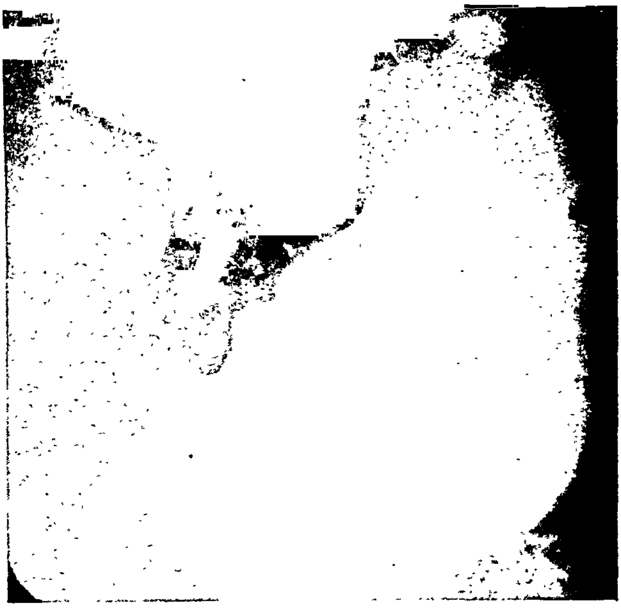

Fig. 4 (case 4).—Roentgenogram interpreted as showing an annular constricting ulcerative carcinoma of the pyloric canal, cytologically negative.

Case 4.—A 54-year-old woman was admitted to the hospital in December, 1956, complaining of a recurrent burning sensation in the epigastrium of 14-months duration. She had consulted her local physician and was told that she had nervous indigestion. Because of the persistence of pain and recent onset of nausea and vomiting, she was hospitalized. Physical examination gave essentially negative results except for epigastric tenderness.

Laboratory studies revealed a red blood cell count of 4,000,000 per cubic millimeter and a hematocrit value of 35 vol.%. A series of tests on the upper part of the gastrointestinal tract (fig. 4) was thought to reveal an annular constricting carcinoma of the pyloric canal. On repeat examination this was again the opinion of the radiologist. Gastroscopy was then performed, and although the ulcerating lesions of the prepyloric area could not be well visualized, the pyloric channel was visualized, and there appeared to be no regal distortion or infiltrative process. On the basis of these findings, gastroscopists felt that we were dealing with a benign lesion. Gastric cytological studies were carried out, and findings were reported as negative. Gastric analysis revealed a normal secretory function of the free and fasting acids. Surgery was advised because of the suspicious roentgenographic findings, and at the time of surgery, the operating surgeon, on opening the specimen, stated that, after gross examination of the specimen, we were dealing with a malignant ulcer. However, the pathological survey proved it to be a benign prepyloric ulcer.

Technique

Patients suspected of having gastric malignancy are subjected to the following diagnostic procedures.

Preparation of Patient.—The patient is given a clear liquid diet on the day before the test. He is to drink five glasses of water before retiring on the evening before the test. Breakfast is not given on the morning of test, but patient is instructed to drink five glasses of water if possible.

Intubation and Lavage.—A 16 F. Levin tube is passed a distance of 60 cm. The entire fasting contents are aspirated, and the fluid obtained is centrifuged, smeared, and labeled "fasting." The lavage solution is prepared immediately prior to use by adding 7 mg. of chymotrypsin to 500 cc. acetate buffer solution (pH 5.6). The solution is instilled into the stomach by the Levin tube. The solution remains in the stomach for 10 minutes, during which time the patient is rotated 360 degrees. It is then aspirated as quickly as possible, centrifuged, smeared, and labeled "#1." The last few drops are then aspirated, centrifuged, smeared, and labeled "#2." As each specimen is collected, the fluid is placed in 50-cc. plastic centrifuge tubes which are on ice. It is necessary that a portable angle head centrifuge be available at the bedside. The solution is immediately centrifuged for three minutes. Sediment used for smearing is placed on one slide. A second slide is placed over the first. The two slides are pressed together and pulled apart. They are placed immediately in ether and alcohol fixative, and then they are stained with the Papanicolaou technique.

Comment.—The slides are then screened by cytological technicians, and the pathologist confirms the diagnosis. The examination is repeated if the specimen is unsatisfactory or if equivocal cells make diagnosis difficult.

Comment

Improved techniques leading to greater accuracy have created more interest in the use of exfoliative cytology in the diagnosis of gastric malignancies.[2] The esophagus, stomach, pancreatic and biliary systems, and the colon have been intensively studied for cancer by use of exfoliative cytology techniques.[1] Experience with this method of diagnosis has proved it to be superior in accuracy to all methods of study, with the exception of surgical biopsy. Usually with this method of study there is little equivocation; either cells which are suspected to be malignant are present or they are not. Infrequently, atypical cells cause the pathologist much concern as to the correct designation. In these cases, a second specimen may help to clarify the problem.

No method of treatment can, at the present time, offer much to patients who have far advanced and usually easily diagnosed cases of cancer of the stomach. It is among the early gastric malignancies that surgery achieves a creditable salvage rate. It is also these early lesions that are missed by roentgenographic studies. Properly performed, gastric cytological studies can produce striking accuracy. The value of cytological diagnosis does not depend on the size of the lesion. In any given case, however, we feel that it is absolutely necessary to apply an over-all diagnostic approach. We use not only exfoliative cytological studies but x-ray studies, gastroscopy, gastric analysis, a good history, and physical examination. The sum total of the accuracy of these diagnostic methods is greater than the accuracy of any one test alone. Of 300 cases the methods and numbers of erroneous diagnoses are as follows: cytology, 7; x-ray, 22; gastroscopy, 14; and over-all diagnostic approach, 3. Using all methods of diagnosis and evaluating them collectively in each individual case, we found that the accuracy was 99.3%.

Summary

Three hundred consecutive patients with symptoms in the upper gastrointestinal tract have been studied, with use of all clinical and laboratory means available. Exfoliative cytological studies proved to be the most accurate individual test. Collective evaluation of all methods of study produced a greater accuracy than did any one test. This over-all diagnostic approach will produce earlier lesions for surgical resection and allow earlier institution of medical management for benign lesions.

6448 Fannin (25) (Dr. Arnold).

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THE PATIENT IN COMMERCIAL JET AIRCRAFT

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Four principal areas of difficulty in air travel for patients are air sickness, pressure alterations with ascent to altitude, decreased concentration of oxygen at high altitudes, and anxiety. Diabetics and patients flying after abdominal surgery should avoid air sickness. There are effective antiemetics, and the smoother jet flight will minimize the problem. Patients with intestinal obstruction; pneumoperitoneum or pneumothorax; and ear, nose, or throat disorders may have serious difficulty because of the change in barometric pressure in jet flight. Decreased is inadequately compensated in patients with significant lung disease, cardiac failure, significant anemia, or histotoxic states. Anxiety, oxygenation of hemoglobin at high altitudes which can increase the cardiac work load, is best allayed by the physician-patient relationship and the physician's expressed confidence that the trip will be uneventful. With few exceptions, aeromedical problems of jet flying are similar to aeromedical problems in general, and most patients who can travel at all can travel more comfortably by air.

With the advent of commercial jet aviation, the aeromedical implications of this mode of travel have become of medical interest. Many patients ask whether they can fly on a jet airliner. Armstrong [1] estimated that 3% of airline passengers are ambulant patients. When one considers that there were 49,075,000 passengers on scheduled airlines in 1958,[2] it becomes apparent that a significant number of patients did travel by air, and their welfare is of considerable practical importance.

In general, the problems anticipated with the transportation of ambulant patients in commercial jet equipment are similar to those encountered with pressurized reciprocating engine aircraft, such as the DC-6 or DC-7 series. Therefore, we may briefly review general aeromedical considerations prior to discussing the areas peculiar to jet aircraft.

General Aeromedical Considerations

Two major airlines have had a unique opportunity to transport patients. The Alaskan division of Pan American World Airways often evacuates patients because of the geographical conditions prevalent in that area. Northwest Airlines has transported over 13,000 patients in a single year.[3] These companies have conducted surveys which aid in our understanding of air travel for patients. It has become apparent that most patients make excellent travelers. However, four principal areas of difficulty have been identified: (*a*) air sickness, (*b*) pressure alterations with ascent to altitude, (*c*)decreased concentration of oxygen at high altitudes, and (*d*) anxiety.

Air sickness is a form of motion sickness, with distressing manifestations of nausea, sweating, headache, and vomiting familiar to all of us. For certain patients this may be deleterious; for example, the diabetic who cannot afford the loss of calories and electrolytes or the patient who travels soon after abdominal surgery. Antiemetic medicaments, such as cylizine (Marezine), dimenhydrinate (Dramamine), meclizine (Bonamine), or scopolamine (Hyoscine), are quite effective in preventing this disorder. In the high operational altitudes of jet aircraft smoother flying conditions are usually encountered, and the problem of air sickness will be minimized.

Changes of barometric pressure are encountered as one attains altitude, which should be considered in evaluating a patient. At sea level, the barometric pressure is about 760 mm. Hg, as ascent is made. This pressure decreases progressively, so that at 5,000 ft. it is 632 mm. Hg, at 10,000 ft. 523 mm. Hg, and at 18,000 ft. it is 380 mm. Hg, or about one-half the pressure at sea level.

This loss of pressure is partially counterbalanced by the artificial atmosphere created in a pressurized aircraft. Here the air within the cabin is compressed so that it is more like the atmosphere at ground level than that through which the plane is flying. Pressurization has been so successful that jet aircraft can now fly as high as 23,000 ft. while the cabin pressure remains at sea level, and at a cruising altitude of 43,000 ft. the cabin altitudes are those of around 8,000 ft.[4]

As the barometric pressure decreases, gases contained within the body cavities expand, according to Boyle's law. Thus, a patient with intestinal obstruction may have serious difficulty, as could one with pneumoperitoneum or pneumothorax. As far as ear, nose, and throat problems are concerned, gases will escape from the middle ear and sinuses. In a patient with severe congestion and edema of the nose, as in upper respiratory infections, difficulty occurs on returning to ground level because of the decreased ability of air to reenter these spaces, and pain secondary to "aerosinusitis" and "aerotitis media" can be most discomforting. One should not fly with an upper respiratory infection. If it is un-

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avoidable, nasoconstrictors should be used, and the patient should chew gum or yawn during descent in an attempt to open the eustachian tubes.

As mentioned previously, the barometric pressure is a measure of the concentration of gas molecules. As one ascends, he encounters less pressure and therefore less gas concentration. Oxygen constitutes about 20% of the atmospheric gases and has a partial pressure of 160 mm. at ground level. Here one normally has over 95% of his hemoglobin oxygenated. At 20,000 ft. about 66% saturation occurs.[5] The body attempts compensation, in normal persons, through hyperventilation and an increase in cardiac output, in an attempt to increase the oxygen in the alveoli of the lungs and in the blood. This compensation is adequate in normal persons up to about 10,000 ft. It is impaired, however, in patients suffering from (*a*) significant lung disease, such as emphysema or loss of significant amounts of lung tissue (such as postpneumonectomy); (*b*) cardiac failure, with minimum cardiac reserve at ground level; (*c*) significant anemia (50% reduction or more of hemoglobin level); or (*d*) histotoxic states such as insulin shock, in which tissue oxygenation is already impaired.

Anxiety inherent in travel, and especially in jet air travel, can, in itself, contribute to patient discomfort and some danger. It has been shown that the work of the heart is increased insignificantly by an exposure to cabin altitudes used in commercial air travel.[6] However, anxiety can significantly increase the cardiac work load.

Probably the best deterrent to excessive anxiety is the patient-physician relationship and the confidence expressed by the physician that the patient can make the trip uneventfully. Occasionally, mild sedation prior to boarding the aircraft is indicated. As jet aircraft come into wider use and are more commonplace, the anxiety occasioned by flying in them will diminish.

Air Travel and Types of Disease

Lung Diseases.—The consideration of disorders of the lung centers mainly around the functional ability of this apparatus. Since physiological hyperventilation is the main compensatory mechanism to altitude exposure, an estimation of the patient's ability to hyperventilate within reasonable comfort levels is important. He should be comfortable and at rest in a sitting position and be able to increase his respiratory work load, by such activities as climbing stairs, with reasonable ease. Cyanosis, respiratory acidosis, and cor pulmonale are signs of severe pulmonary disease. While the presence of any of these signs is not an absolute contraindication to low cabin-altitude exposure, possible in some reciprocating engine aircraft, they probably warn of potential difficulty at cabin altitudes of 7,000 or 8,000 ft. which can be expected in jet aircraft. In the case of a patient with severe emphysema with respiratory acidosis, I would not recommend the use of supplemental oxygen in order to raise the altitude ceiling. In the instance of a patient with a restrictive functional defect, such as a postresectional state or pulmonary fibrosis, with some cyanosis, acidosis is uncommon and the patient could be approved for jet aircraft travel, provided oxygen was supplied at operational altitude. Most airlines will provide oxygen if arrangements are made at the time of the ticketing. Acute pathological processes, such as acute pneumonia or an acute asthmatic attack, necessitate postponement of the flight until the condition no longer exists.

Heart Disease.—Two factors must be considered in the patient with heart disease: (1) the increase on the cardiac work load and (2) potential cardiac hypoxia. Experiments have shown that no significant alteration in pulse and blood pressure or cardiac work occurs at the usual operational cabin altitude. Cardiac work increases moderately at 12,000-to-14,000-ft. altitudes.[5] The pulse and blood pressure may also increase significantly during jet take-off if anxiety is present. In patients in conditions under which oxygenation of the myocardium is marginal, such as a recent postinfarctional period or severe angina pectoris, the altitude exposure and stresses of jet flights are contraindicated unless supplemental oxygen is available. Travel in planes which use lower cabin altitudes would be preferred if the flight is necessary. In patients with other conditions in which there is no cardiac failure, the relief of anxiety is important, but I can see no contraindication to jet flying.

Cardiac failure is a contraindication to air travel. The danger of acute pulmonary edema, with its rapid and alarming deterioration of the patient's condition, would complicate the picture by a superimposition of respiratory insufficiency. This condition, however, contraindicates any mode of transportation.

Abdominal Conditions.—The expansion of trapped gases constitutes the main danger here. In a patient with bowel obstruction, gas expansion would compromise the blood supply of the containing bowel wall, with danger of necrosis and rupture. Unreduced hernias must also be viewed with suspicion. A perforated viscus is obviously an absolute contraindication to air travel. The flatulence of patients after abdominal surgery is well known; thus, an air trip could well be postponed until two weeks after such a procedure.

Hematological Disorders.—The presence of a reduced amount of hemoglobin available to convey oxygen to the tissues can be marginally sufficient at sea level. However, at the reduced oxygen tensions of high altitudes, acute tissue anoxia may occur. Thus, a reduction of hemoglobin level of more than 50% or a reduction of the red blood cell count below 2,500,000 per cubic millimeter are contraindications to exposures to jet aircraft cabin altitudes. If a transfusion is given to raise the erythrocyte or hemoglobin level, a trip should not be made prior to 48 hours after the transfusion to assure the absence of hemolysis.[7]

One hematological condition which is peculiar at high altitudes is the sickling trait, present in about 7% of Negroes. Splenic infarction has been reported as clinical sickling becomes overt at the reduced oxygen tensions of high altitudes. Thus, the presence of the sickling trait is a contraindication to jet flights. Patients with leukemic disorders can travel by jet aircraft safely if the red blood cell counts and hemoglobin determinations are within acceptable levels or are transfused to these levels.

Pregnancy.—Pregnant women may fly without question during the first seven months of a normal pregnancy. They can fly during the eighth and ninth months if they furnish a statement from the attending physician that they are not due to deliver within five days of their departure from the plane.[8] Cabin altitudes of jet equipment should have no untoward effects on the pregnancy.

Infants.—It is usually advisable for infants delivered at term not to fly at less than 7 days of age, because of the immaturity of their respiratory apparatus. After this, the airlines have had no difficulty carrying these babies. Nursing of infants during the descent in flight helps maintain the patency of the eustachian tubes and prevents aerotitis media.

Contagious Diseases.—Patients with the usual contagious diseases, such as diphtheria, measles, mumps, whooping cough, scarlet fever, and tuberculosis are regulated in air travel as in other travel involving interstate traffic. They come under the jurisdiction of the foreign quarantine service of the United States Public Health Service and are not acceptable for air travel at any time.[9]

General Consideration of Patients in Airline Travel.—The condition of the patient must be such that he will demand little more attention from the stewardess than the routine passenger. If he cannot fulfill this requirement, he must be accompanied by an attendant with whose help he will qualify in this respect. His condition must not be personally offensive to fellow travelers, e. g., malodorous or nauseating. He must not be a source of danger to the security of fellow passengers, e. g., an aggravated psychotic. He must not be a source of infection nor contagious to the fellow passengers confined with him in the close quarters of a plane cabin.

Minimal first aid is available to him at the hands of the crew members or cabin attendants. However, emergency medical care generally is as remote as the medical facilities at the nearest airport.

Special Considerations of Jet Aircraft Travel.—The acceleration of jet airplanes on take-off is significantly greater than that of the piston engine aircraft. However, other than a definite "settling back in the seat" the sensations are minimal and not dangerous.

The rates of climb and descent are greater in jet aircraft because of the high fuel consumption at low altitudes and the efforts to lessen noise to ground areas around airports. While the effects of rapid ascent and descent are minimized by excellent cabin pressurization, the expansion of gases within the body cavities is somewhat more rapid. Thus, greater efforts must be made to open eustachian tubes.

The cruising altitudes of jet aircraft are significantly higher than those of the piston engine aircraft, so that air turbulence is minimized and the flight is smoother. Also, vibrations secondary to the reciprocating engines are absent. This lessens the tendency toward air sickness and adds to passenger and patient comfort. Since the travel time between two given points is significantly shorter, a smoother trip performed in a shorter time results in a less weary passenger debarking from the jet airliner at his destination.

Summary

About 3% of airline passengers are ambulant patients. There is every reason to believe that more and more ambulant patients will fly in the future and that they will and should turn to their physicians for advice in this matter. In evaluating such a patient, the physician should formulate an opinion of the patient's ability to travel by air, specifically by jet aircraft. With few exceptions, the aeromedical problems peculiar to jet flying are similar to aeromedical problems in general, and an understanding of these will greatly aid in evaluation of the patient. Most patients who can travel at all can travel by air more comfortably and with less exhaustion.

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CLINICAL NOTES

CUTANEOUS FILARIAL INFECTION IN HUMAN BEINGS

Vincent T. J. Lenth, M.D., Jacksonville, Ill.

Only rarely does one have the opportunity to observe a cutaneous filarial infection in the United States. A review of the literature reveals that such lesions have been observed only in widely separated areas throughout the world. Faust[1] summarized the reports of authorities from various countries and recorded 37 cases of unusual filarial infection. Twenty-nine of these were identified as due to "dirofilaria, sub-genus nochtiella conjunctivae." Most of the cases originated in southern Europe and the eastern Mediterranean countries. Isolated specimens were obtained from Asia (two), Africa (two), the United States (three), and Argentina (one). Most of these lesions were manifested in single cutaneous nodules. A few involved some of the more highly specialized structures such as the orbit, cornea, and eyelid. In a few instances, the filaria exhibited migratory characteristics, the pathways of which could be traced.

All of the cases from the United States, as reported by Faust, had their origin in Florida, two in West Palm Beach and the third in Jacksonville. Subsequent to his report in 1957, two additional cases from the Miami area in 1959 were reported by Sams and Beck.[2] A report of what is believed to be the sixth such case follows.

Report of a Case

On Sept. 26, 1959, a 65-year-old woman from Illinois who for the past four years had been residing at Sarasota, Fla., was seen, complaining of a small ulcerated swelling on the right side of the chest, immediately above the breast. About two months earlier she recalled having been stung by an unidentified insect. Subsequently she became aware of a painless swelling, bluish-red in color. There was occasional slight itching at the site of the lesion. A few days prior to examination ulceration developed, accompanied by a scanty watery discharge. When undisturbed, a slight crust would form over the opening. There were no other attendant symptoms. There was no history of adenopathy at any time during the two-month period, and the patient stated that she had felt quite well.

Examination of the skin of the chest wall on the right revealed a nodular lesion about 15 mm. in diameter and elevated about 5 mm. The lesion was of a purplish-red color and the margins were well defined. The central area was covered by a slight crust, and when this was wiped away a fine, glistening, thread-like filament was seen to protrude about 5 mm. from the wound. This was grasped with a forceps and a filarial parasite, about 5 cm. in length, was removed. After its removal slight movement was noted. A similarly discolored area, 3 to 4 mm. below the previously described lesion, was also observed, but no ulceration was present. Subsequently, a biopsy of both lesions was made at Our Saviour's Hospital and the pathologist, Dr. Hugh A. McKinley, diagnosed the lesions as granulomas. Cross sections of filarial organisms were not observed in any of the specimens.

Since it was impossible to identify positively the species of filaria, the assistance of the Communicable Disease Center, Chamblee, Ga., was enlisted; after study of the specimens, Dr. George Healy replied, "The filarial worm which was recently submitted has been identified as probably *dirofilaria spp., subgenus nochtiella conjunctivae.*" The worm was an immature female.

Thus far, the literature seems to support the supposition that cutaneous filarial infections in human beings are the exception in the United States rather than the rule. Faust[1] stated that "The method of human exposure to species of *dirofilaria* has not been elucidated but it seems probable that the cycle involves an insect vector (most likely a mosquito), which inoculates the infective stage into the human host. This is typically a 'dead-end' cycle, since there is thus far no evidence that viable microfilarias are produced by dirofilarias in the human host." He has suggested that D. conjunctivae may be D. immitis in an abnormal host. The latter is the heartworm of dogs and is mosquito-borne. Human beings in the Florida area are repeatedly bitten by these same mosquitoes. Physicians who see patients from Florida should regard with suspicion small cyst-like cutaneous lesions.

Summary

A case of infection with Dirofilaria conjunctivae in a human being is the sixth such case to be identified in the United States. Although this is the first one observed and reported in Illinois, it must be concluded that the infection originated in Florida.

200 W. State St.

Dr. James O. Bond, Director of the Bureau of Preventable Diseases, Florida State Board of Health, assisted in the preparation of this report.

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INTESTINAL LIPODYSTROPHY WITHOUT DIARRHEA

REPORT OF A CASE DIAGNOSED BY INTESTINAL TUBE BIOPSY

Marion D. Hargrove Jr., M.D., John V. Verner Jr., M.D.,
R. L. Patrick, M.D.
and
Julian M. Ruffin, M.D., Durham, N.C.

Increasing interest in intestinal lipodystrophy (Whipple's disease) has been shown during the past year, with two series of six and seven cases, respectively, having been reported.[1] These represent about one-fifth of the accepted cases reported in the world's literature since the original description of this disease by George Whipple in 1907.[2] Evidence suggests that intestinal lipodystrophy is more than a local disease of the small intestine. Typical pathological changes may be found not only in the intestinal mucosa and mesenteric lymph nodes but in peripheral lymph nodes as well.[3] Indeed, serous cavities may be involved, and bacterial vegetations in the endocardium are not rare.[4]

A highly characteristic clinical picture usually is present. This includes diarrhea, steatorrhea, arthralgia, lymphadenopathy, abdominal pain, and weight loss. One or more of these manifestations may be absent, but, generally, all will develop during the course of the disease.

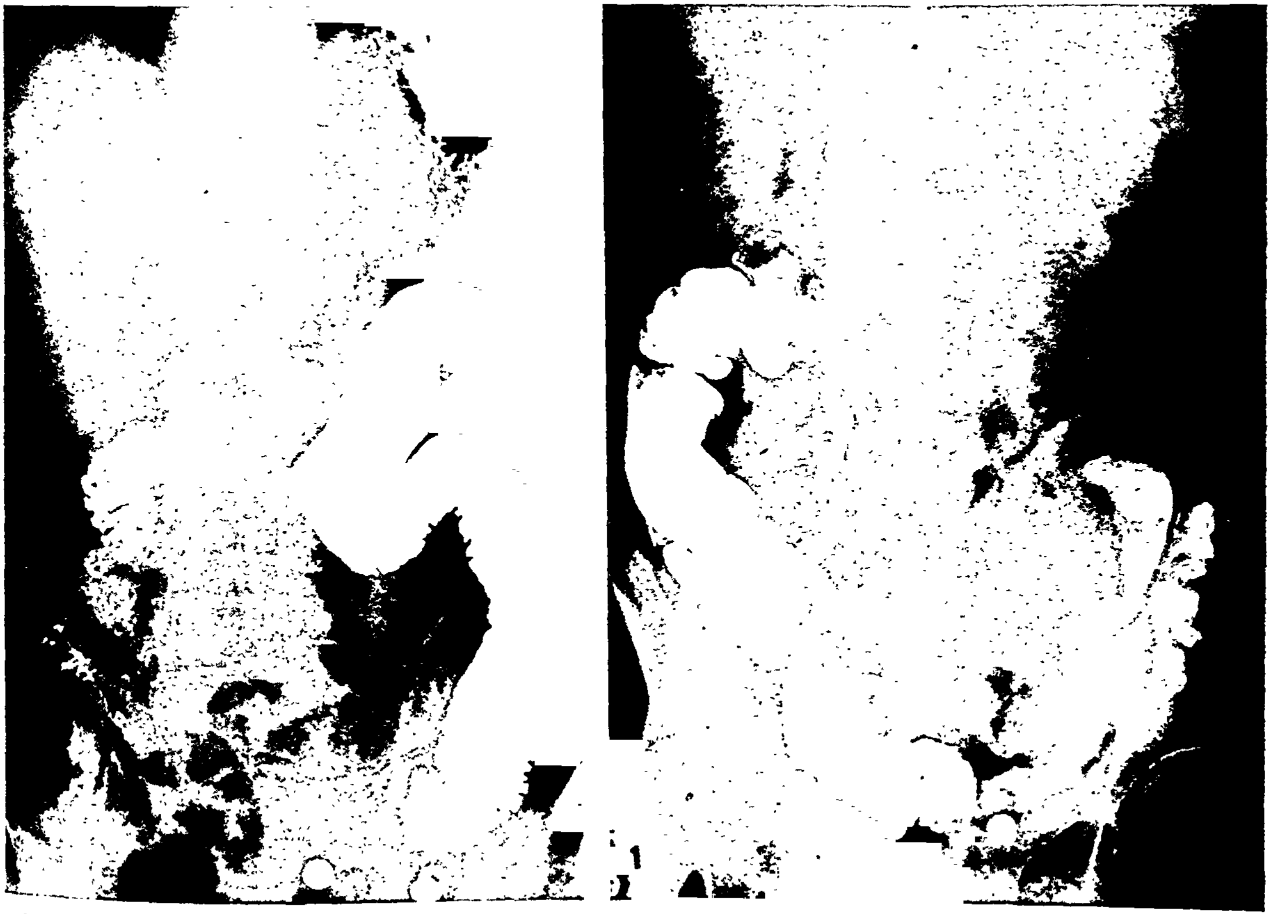

Fig. 1.—Roentgenogram of abdomen showing (*left*) mucosal edema, widening of the jejunum, and long dilated segment of jejunum and (*right*) changes in the terminal ileum, with narrowing and suggestion of thickening of the bowel wall.

The patient reported here was of unusual interest because of the absence of diarrhea or gross steatorrhea, the prolonged course of fever of unknown etiology, and, finally, the ease with which the diagnosis was established by peroral biopsy of the jejunal mucosa.

From the departments of medicine and pathology, Duke University Medical Center.

Report of a Case

A 47-year-old man entered Duke Hospital on May 28, 1959. His illness had begun with the gradual onset of weakness, malaise, weight loss, and anorexia seven months prior to admission. He was hospitalized elsewhere at that time, and no abnormalities were found except for a leukocyte count of 16,000 per cubic millimeter and a slight elevation of temeprature, 99 to 100 F (37.2-37.7 C). After discharge, he remained about the same until March, 1959, when he was readmitted because of increasing weakness and an additional 5-lb. (2.3-kg.) weight loss. At this time, his hemoglobin level had dropped from normal to 10.5 Gm.% but the findings of the remainder of the examination, including x-ray of chest, gastrointestinal series, and bone marrow studies were entirely negative. An exploratory laparotomy, performed on April 13, revealed a large mass of mesenteric lymph nodes; a biopsy of these nodes revealed granulomatous inflammation. Postoperatively, he developed a spiking fever with temperature to 106 F (41 C), which was unaffected by administration of tetracycline and chloremphenicol, a two-day course of nitrogen mustard (0.4 mg. per kilogram of body weight) or x-ray therapy to the abdomen, daily for seven days. Repeated blood cultures taken before institution of therapy were all negative. Two transfusions of whole blood were given because of the patient's increasing anemia. He had now lost 19 lb. (8.6 kg.) and, for the first time, complained of vague, mild, upper abdominal pain. Because of the patient's progressive downhill course, he was transferred to Duke Hospital for further evaluation.

The patient had had an episode of acute polyarthritis 13 years ago and intermittent arthralgia since that time. No other members of the family were similarly affected.

On examination, he appeared chronically ill, emaciated, and depressed. The blood pressure, taken with the patient in supine position, was 110/60 mm. Hg, with a postural drop of 15 mm. A generalized increase in pigmentation was observed, especially over the recent surgical scar. There was no significant peripheral lymphadenopathy. The abdomen was tense and distended, with generalized resistance to palpation. There was no evidence of fluid, and no definite masses or organs could be palpated.

X-rays of the chest, stomach, and duodenum were normal. A small-bowel study (fig. 1) showed mucosal edema, thickening of the bowel wall, narrowing of the terminal ileum, and a long dilated loop of jejunum in the upper abdomen.

An L. E. test, routine agglutinations, as well as fungus and tuberculin skin tests gave negative findings. Cultures of the blood, urine, bone marrow, stool, and liver-biopsy material were likewise negative, as were complement fixation tests for blastomycosis, histoplasmosis, and coccidioidomycosis. Results of repeated stool-guaiac tests and urinalyses were negative.

The pertinent laboratory findings were as follows: hemoglobin level, 9.4 Gm. %; white blood cell count, 13,375 per cubic millimeter, with a normal differential count; serum albumin level, 2.4 Gm. %; serum globulin level, 4.2 Gm. %; total serum cholesterol level, 256 mg. %; serum phosphorus level, 4.3 mg. %; serum calcium level, 7.5 mg. %; blood urea nitrogen level, 15 mg. %; fasting blood sugar level, 103 mg. %; serum potassium level, 4.7 mEq. per liter; serum chloride level, 100 mEq. per liter; serum carbon-dioxide level,25 mEq. per liter; and prothrombin concentration, 94% of normal.

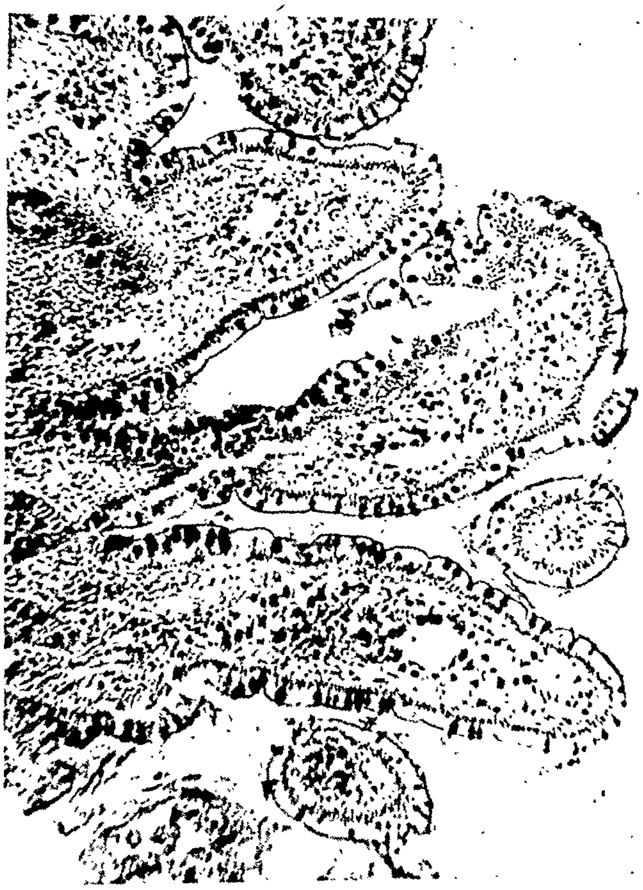

Fig. 2.—From peroral jejunal biopsy. Widened villi and numerous macrophages in lamina propria contain PAS-positive material (× 97).

A jejunal biopsy specimen showed numerous macrophages containing PAS (periodic acid-Schiff) positive material (fig. 2). A review of the lymph node biopsy specimen obtained at the previous operation, likewise, showed changes typical of intestinal lipodystrophy (fig. 3). A liver biopsy specimen was normal. I^{131}-triolein blood levels were 7.1% at 4 hrs., 7.1% at 5 hrs., and 6.9% at 6 hrs., indicating slight impairment of fat absorption.[5]

At Duke Hospital the patient was given an eight-day course of penicillin and streptomycin, and he received corticotropin (ACTH gel), 40 units in 1 cc., twice daily, for three weeks. During this time, he became afebrile and gained 16 lb. (7.3 kg.) (fig. 4). When corticotropin therapy was discontinued, the fever and abdominal pain recurred. Therefore, he was given dexamethasone, 5 mg. per day, followed by a maintenance dose of 3 mg. per day. He was discharged on July 12, greatly improved. At no time had there been any diarrhea.

When the patient was seen two months later, he had gained 35 lb. (15.9 kg.); his appetite was excellent; and he was relatively symptom-free.

Comment

The patient whose case is reported here had an illness characterized by fever of unknown origin for eight months before the diagnosis of intestinal lipodystrophy was established by peroral intestinal tube biopsy. A similar case of intestinal lipodystrophy with recurrent fever of unknown origin of three and one-half years duration has been reported recently.[1b] The correct diagnosis in this case was made by lymph node and intestinal biopsies, obtained at exploratory laparotomy.

It has been stressed repeatedly that diarrhea is a prominent manifestation of the disease, although it has been reported that constipation may persist throughout the entire illness.[1a] In our patient, there was no diarrhea; in fact, he often required laxatives for constipation. The point has been made[6] that diarrhea has been present in every case where pigmentation is marked. In this patient, on the contrary, pigmentation was a striking feature, being most marked over a surgical scar.

Although intestinal lipodystrophy may be suspected on clinical grounds, the diagnosis depends on lymph node or intestinal biopsy. In the past, it has been customary to perform an exploratory laparotomy on the patient and obtain a mesenteric node or a section of small bowel. The availability of an instrument by which a peroral intestinal biopsy can be made should obviate the need for surgery. We have used the instrument and technique as described by Shiner[7] and have found it to be a safe and simple procedure. Since the intestine is diffusely involved in intestional lipodystrophy, it provides and excellent target for an essentially blind biopsy. The mucosal changes typical of the disease are demonstrated in figure 2. Two earlier cases have been diagnosed by peroral intestinal tube biopsy.[8] To our knowledge, this is the third patient in whom the disease has been diagnosed by means of this biopsy technique.

Another notable feature of this case was the gratifying response to steriods and antibiotics. In the three months since therapy was begun, the patient has gained over 50 lb. (22.7 kg.) and is clinically

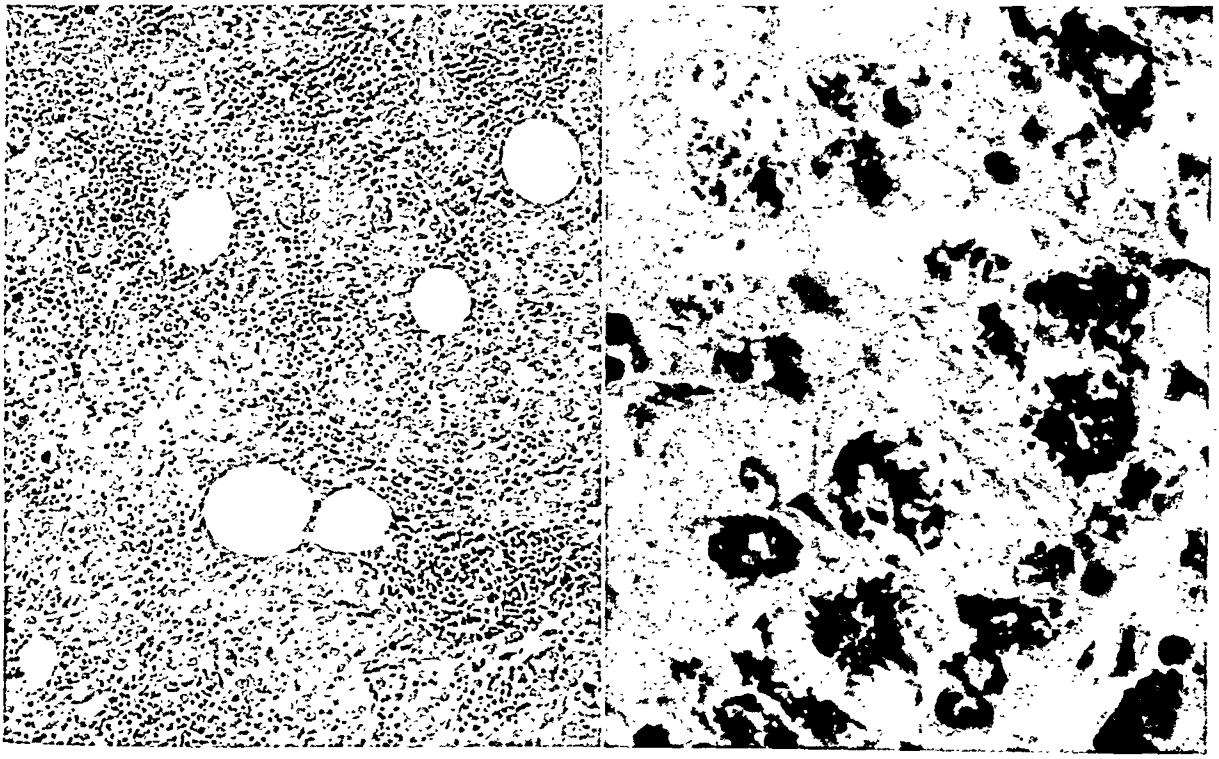

Fig. 3.—*Left*, remarkable accumulation of foamy macrophages in mesenteric lymph node. There are also scattered cystic spaces. Hematoxylin and eosin stain (× 137). *Right*, characteristic particles in macrophages in lymph node. Periodic acid–Schiff stain (× 893).

in remission. Varying results with the use of ACTH and steriod therapy have been reported.[9] Temporary and even long-standing remissions have been seen. Paulley[10] reports a case showing dramatic improvement after two courses of chloramphenicol. We have three additional patients who are alive and well 30 to 52 months after the diagnosis was made. These results suggest that intestinal lipodystrophy is not necessarily fatal and that, if the patient can be tided over a critical period of malnutrition, recovery may take place.

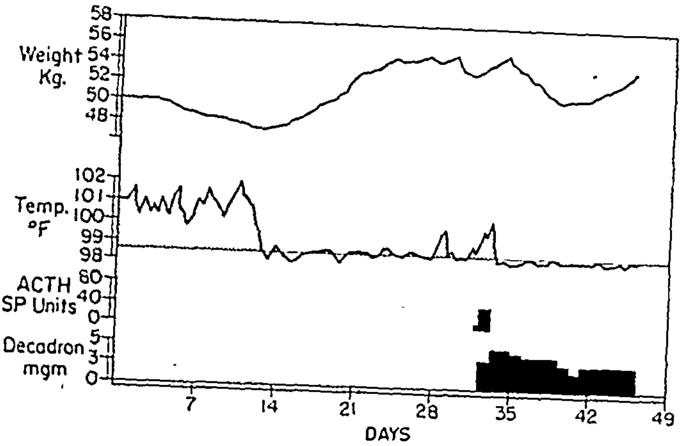

Fig. 4.—Patient's clinical course in hospital.

Summary

An unusual case of intestinal lipodystrophy (Whipple's disease) occurred in a patient in whom diarrhea never developed; the presenting problem was fever of unknown origin. To our knowledge this is the third patient in whom the diagnosis of intestinal lipodystrophy was made by peroral intestinal biopsy. The response to steroids and antibiotics was gratifying, indicating that the disease is not necessarily fatal.

This study was supported in part by a grant from the National Institutes of Health.

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SCHOLARSHIP IS A PROFESSION.—In this it resembles law, medicine, museum works, acting, personnel management, the ministry and other vocations. Its point of view is as essential to the total national picture as is the point of view of any other profession from that of war to that of the ministry. To infer or assume, as some have done, that scholarship is an escape from reality into a sort of never-never land is an inexcusable error. Scholarship is not an escape from reality; it is a part of reality, it is reality, since, if there were no scholarship, it would be hard to think of us as a nation. There would be no art museums, libraries, theaters, parks, or holidays, just as there would be no formal religion, no laws, and no courts. Without scholarship, there is no history, and no tradition, and no notion of the meaning of words like "justice," "right," "fair practice," "contract," "beauty," "the Christian tradition," "authority," or "the United States."—Howard Numford Jones, One Great Sociey, Harcourt, Brace and Company, New York, 1959.

AN IMPROVED URINAL

Blaine C. Collins, M.D., Memphis, Tenn.

The management of urinary incontinence is still a difficult problem in many patients. This is especially so in the patients who have been afflicted with this condition for a prolonged period of time and cannot or will not tolerate the Foley type catheter. The proprietary types of rubber urinal leave much to be desired, and many patients will not tolerate them.

The unconscious or comatose patient presents less of a problem in this regard as the Foley catheter can be used here and the patient does not complain. However, a patient who is fully rational and otherwise in no acute discomfort will often not tolerate it for the period of days or weeks which it may be needed.

We have found that a very satisfactory appliance can be fashioned from a condom and a length of rubber or plastic tubing. A small opening is made in the end of the condom and the tube inserted and securely fastened to the condom by the use of a small rubber band around the condom over the tube. The open end of the condom is then placed over the glans penis and secured with a bit of elastic tape if necessary.

Patients who have used this appliance have been grateful as a result. One patient recently told me that he had his first full night's sleep after using it for the first time.

3144 Summer Ave.

SLEEP PARALYSIS WITHOUT NARCOLEPSY OR CATAPLEXY

REPORT OF A CASE

Jerome M. Schneck, M.D., New York City

Almost invariably sleep paralysis is reported in combination with narcolepsy and cataplexy. During the past 12 years I have encountered at least six patients with sleep paralysis alone. Narcolepsy or cataplexy were not concurrent, nor was a history of either elicited. Patients generally do not seek help for sleep paralysis in isolation, and as a matter of fact the symptoms apart from those of the narcoleptic triad are apparently not often correctly diagnosed. The dramatic aspects of narcolepsy are more readily identified. When sleep paralysis is mentioned in publications it is usually included in articles stressing narcolepsy.[1] Only a few articles published during the past 20 years have given special attention to various aspects of sleep paralysis, such as psychodynamics and treatment.[2] Since the diagnosis of sleep paralysis appears to be missed often, the affliction probably is more widespread than general physicians and specialists realize.

Sleep paralysis occurs when a person is falling asleep or awaking. The patient often refers to having felt partially awake and partially asleep. The inability to move is dispelled at times by merely a slight touch. Accompanying the paralysis there is usually a feeling of anxiety, and there may be hallucinations. Frequency of attacks varies considerably. The patient is usually aware of his environment, but time may undergo distortion. He is generally unable to speak during the attack. The paralysis lasts several seconds or minutes.

The most recent consultation in which I encountered sleep paralysis is being reported for several reasons. The descriptive features of this problem are very clearly delineated. The attacks were so severe that the patient sought an opinion specifically about the sleep paralysis; in most other cases the issue of sleep paralysis is discerned as a secondary item among primary complaints. This case highlights the sleep paralysis without concurrent narcolepsy or cataplexy.

A 27-year-old woman requested psychiatric consultation for repetitive nightmares of a special type. On falling asleep or awakening, she would find herself completely paralyzed. She would feel partially awake and partially asleep and would manage to open her eyes partially. She would feel someone climbing onto her bed and on top of her. (I have encountered this impression in other patients with sleep paralysis.) The pressure of this weight on her would be great, yet no one could be seen. She would feel at times that the person was a man and at other times a woman. Then she might feel herself being strangled by this person. As her eyes remained open she would hallucinate other figures in the room. These were of two types: the first consisted of giant-sized, headless men, and the second comprised giant-sized but ill-defined animals. She could offer no additional descriptions. The figures would move slowly toward her, never reaching her. and the passage of time seemed interminable. She would attempt ineffectively to shout, but at most she would be capable of moaning. She would be aware of her surroundings, knowing for example that her daughter was home, hearing her; she could even listen completely paralyzed to the television programs that her daughter was watching. She would make unsuccessful efforts to move her head and arms. Suddenly her attacks would terminate

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From the Department of Psychiatry, State University of New York College of Medicine.

spontaneously. The hallucinations would end, the anxiety ease, and the paralysis disappear. On occasions her daughter or husband might hear her moan, touch her, and abort the episodes. The intense anxiety would be accompanied by fear of imminent death.

The patient sought help because the attacks were appearing with increasing frequency. She was experiencing them almost every day. Through the years she had been troubled by them every few days, weeks, or months. A year never passed without them. They had started as far back in childhood as she could recall, at least at the age of 5 and 6 years. The repetitive pattern was unaltered, while other nightmares constantly varied in content and feeling. She was questioned carefully about the symptoms of narcolepsy and cataplexy but denied any such experiences.

Psychotherapy was recommended for this patient. The history offered in consultation revealed a childhood involving extreme insecurity and separation from parents. She appeared to harbor feelings of considerable helplessness mixed with great hostilities and frustrated rage. It may be conjectured that they found symbolic representation in the peculiar symptomatology outlined here.

Summary

A 27-year-old woman had symptoms that clearly delineated the pattern of sleep paralysis. The report is of interest as the sleep paralysis, because of its severity, was offered as a primary rather than a secondary complaint. In addition it highlights the occurrence of sleep paralysis without concurrent narcolepsy or cataplexy; this is contrary to presentations emphasizing the dramatic aspects of narcolepsy, with sleep paralysis a more occasional or incidental finding. As one of a series of such cases, it is clear that narcolepsy or cataplexy may be accompanied by sleep paralysis, but sleep paralysis need not necessarily be accompanied by narcolepsy or cataplexy.

26 W. 9th Ave. (11).

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CIGARETTE SMOKING AND CARDIOVASCULAR DISEASES

In 1957, the American Heart Association issued a statement on smoking and cardiovascular diseases.[1] Among other things, this statement indicated that the available evidence at that time was not sufficient to justify conclusions concerning a cause and effect relationship between cigarette smoking and increased death rates from coronary heart disease.[2] Since then, sufficient additional knowledge has accumulated to warrant a new report on cigarette smoking and its possible relationship to cardiovascular diseases.

Up to the present time, a number of medical studies have been completed, nearly all of which demonstrate a statistical association between heavy cigarette smoking and mortality or morbidity from coronary heart disease. In these studies, death rates in middle-aged men from coronary heart disease were found to be from 50 to 150% higher among heavy cigarette smokers than among those who do not smoke. This statistical association does not prove that heavy cigarette smoking causes coronary heart disease, but the data strongly suggest that heavy cigarette smoking may contribute to or accelerate the development of coronary heart disease or its complications.

Because coronary heart disease is the leading cause of death and a major cause of disability in the American population, the American Heart Association believes that these studies concerning cigarette smoking and coronary heart disease should be called to the attention of the medical profession, allied health professions, health educators, and the general public. The Association recognizes the need for more knowledge and will continue to encourage systematic biological and medical research in order to determine whether a causal relationship exists between cigarette smoking and coronary heart disease and also to determine the effects of smoking in relation to strokes and other important aspects of cardiovascular diseases.

Supporting evidence for the statement above will appear in the July 1960 issue of Circulation, *one of the official journals of the American Heart Association.*

1. Ad Hoc Committee on Smoking and Cardiovascular Disease: L. N. Katz, M.D., Chairman, Chicago; E. V. Allen, M.D., Rochester, Minn.; M. Cherkasky, M.D., New York; F. W. Davis, M.D., Baltimore; T. R. Dawber, M. D., Framingham, Mass.

2. Smoking and Health: Joint Report of Study Group on Smoking and Health, Science **125:**1129, 1957.

COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.
H. D. Kautz, M.D., *Secretary.*

STATUS AND PROSPECT OF DRUGS FOR OVEREATING

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A unified statement on the pharmacotherapy of obesity is difficult to make, largely because, even as a symptom—to say nothing of it as a syndrome, obesity implies neither a specific disturbance in physiological function nor a specific physical abnormality; rather, it is a consequence of a variety of nonrelated etiological factors. There is only one feature common to most instances of obesity, that of caloric intake in excess of normal energy requirements. Since this discrepancy provides both a clear and a tangible point of attack, it is the usual target.[1] Hence, rather than to consider the effect of drugs in obesity, it is more realistic as well as more practical to consider the drugs at hand for controlling overeating.

Although studies in the laboratory and observations of animals in their natural environment have not elucidated the appetite mechanism, they seem to indicate adequate natural homeostatic arrangements to relate appetite to physiological needs for food.[2] The eating patterns of most modern human adults, however, are so distorted that appetite drive and specific food selection appear to have little to do with energy and metabolic requirements.[3] Customs of diverse subcultures enter into the motivation for eating patterns; the physical configuration one cultural group considers pleasing another considers ugly; what one set feels has porcine or boorish implications another considers representative of virility or opulence. In our own subculture, social protocol also complicates matters.[4] The business luncheon with cocktail, the before-meal highball or two or three, the with-highball canapés, all are part of the mores which consider the slim figure desirable but provide eating customs which make it hard to achieve.

Psychological factors are also concerned in the kind, amount, and frequency of eating.[5] Many people eat more when they are bored than when they are busy. Some persons eat more when they are anxious than when they are at ease, and, conversely, some persons lose appetite when under tension; others cannot sleep shortly after eating, but many find the bedtime snack has a "sedative" action and cannot fall asleep without it; still others raid the refrigerator whenever sleep is disturbed.[6] When the latter condition is well developed, it is given status by a psychiatric designation, the "night-eating syndrome,"[7] but compulsive eating also commonly occurs during the day. None of this eating can be presumed to be in response to normal stimulation of an appetite-control mechanism.[8]

Although hereditary predisposition appears to be important in some persons, this is often difficult to distinguish from culturally based obesity. Genetic, glandular, and other physical and physiological causes play a statistically small role in obesity, probably in less than 10% of all cases.[9]

It may also be a fact that most persons who regularly overeat do not attempt to achieve satisfaction of the appetite per se but eat compulsively much as the alcoholic person drinks compulsively.[10] Just as the latter does not stop his drinking when he has attained what others might consider a pleasant state of inebriation but continues on to stupor, so the compulsive overeater often continues stuffing himself beyond satiation, and sometimes he does so until it becomes physically unpleasant to eat more food. If more were known about the normal appetite mechanism, perhaps something more rational and lasting could be done about it pharmacologically. However, although we have many hypotheses, neither the central site nor the precise mechanisms of normal appetite control are yet definitely established.

Approach to Therapy

Today it is more common to treat the patient's obesity on the basis of intake rather than output.

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Thus, the popular therapeutic approach is to contrive to have the obese patient eat less, whereas it is far less common to increase his metabolic rate or to depress his ability to assimilate the food he ingests. It is generally conceded that the first procedure is the safest as well as the most practical method.

The problem of judging the effects of drugs and regimens in the treatment of obesity is seriously complicated by the psychological issues involved in abnormal eating patterns. In the beginning of therapy, almost any regimen applied with sufficient suggestion will have some effect. Thus, Adlersberg and Mayer [11] showed in a long-term study that excellent results were obtained during the early stages of almost all types of treatment, reflecting, in a large part, both the early willingness of subjects to cooperate with a new physician and the psychological impact of a new therapy.

The findings of Stunkard bear heavily on the ultimate value of the pharmacological approach.[12] In a large number of obese patients, Stunkard found that only 12% followed treatment long enough to experience significant weight losses. Furthermore, half of these had regained their weight at the end of one year, and, at the end of the second year, only 2% of the original group had maintained their weight losses. He found that about half of the persons on the weight-losing regimens had suffered some psychic reactions to it, and half of these reactions were severe emotional disturbances.[13] It seems clear from these results that, along with the weight-losing regimen, an adequate substitute must be provided for the psychological satisfaction which the obese person derives from overeating.

Since psychogenic factors are so important, there are many physicians who are inclined to believe that the best hope for sustained results from therapy lies in the psychological approach to overeating.[14] They point to the fact that the best long-term results (about 50% sustained improvement) have been reported from this form of treatment.[12c] Group therapy for obesity has already been successfully instituted.[15] Self-help groups are also in operation.[16]

Pharmacological Agents for Hyperphagia

The agents used for hyperphagia may be divided into (1) central appetite depressants, (2) central-stimulating appetite distractors, (3) metabolic stimulants, (4) sedatives and tranquilizers, (5) bulk producers, (6) purgatives and diuretics, and (7) miscellaneous devices.

Central Depression of Appetite.—True depression, i. e., direct central depression of appetite, occurs regularly in disease, as in hepatitis, and as the undesirable consequence of other therapies, for example, digitalis overdosage. Although this type of depression of appetite is a common cause of weight loss, even if it were safe as a therapeutic approach, it is not likely to be pursued because it is associated with distress. Whether true central depression of appetite can be dissociated from nausea or a "sick" sensation remains to be demonstrated. If such a drug effect were deliberately induced, after the depressive effect on the appetite was lifted lost weight would be regained as the patient responded to his rejuvenated appetite drive. Such an effect of a drug on appetite is not now consciously used in the treatment of obesity.[17]

Central-Stimulating Appetite Distractors.—The mainstay of current pharmacotherapy of obesity is the so-called anorexigenic (anorexiant, anorectic, or anorexic) drug. The terminology is unsatisfactory, however, because it is probable that none of the drugs in common use to which the words are now applied are true central appetite depressants; therefore, they are not really anorexigenic, and none of the terms is a proper portmanteau word for the drugs on hand. However, the effect of the central stimulants which decrease hyperphagia is acceptable to the patient, and he is likely to continue taking the drug. This is largely because, in the use of this group of drugs, the patient's abnormal drive for food is distracted by a sense of well-being or "lift." [18]

Amphetamines.—When given in sufficiently large doses, the sympathomimetic amine-type of central stimulant will depress eating in normal man and laboratory animals; in the usual clinical doses, these agents do not uniformly depress the appetite in all who overeat. Therefore, they may have little or no effect at all on the normal appetite, although central stimulation resulting in anxiety, increased mental and physical activity, and insomnia are regular consequences of these agents. The indications are that the desire to eat is eased because of the central stimulation. Many patients clearly experience and distinguish a pleasant effect or "lift," [18] and the distraction from hyperphagia is thought to be secondary to it.[19] On the other hand, in bulimia after frontal lobotomy these drugs do not depress appetite.[20] Central stimulation, not a specific central depressant effect on appetite, is then the common mechanism through which these drugs act; it is clear, therefore, why undesirable central stimulant effects, which have constituted their chief clinical limitation, have thus far appeared to be indivisible from anorexigenic action.

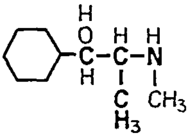
A loss of acuity of olfactory and gustatory sensibility has also been described, which may conceivably contribute to appetite depression.[19b] Although denied by some physicians, it has been suggested that the increased physical activity also helps, not only through its modest calorigenic effect but also because activity per se sometimes seems to alleviate the drive to overeat.[21] The degree of depressant effect on gastrointestinal activity is not considered significant.[22]

In any event, it seems clear that the combined effects do not produce appetite suppression in obese persons sufficiently to make them lose weight without simultaneous dietary control.[23] Gelvin and others state that, "the role of the anorexigenic agents is that of a 'crutch'; their use should be eliminated as early in the therapeutic program as possible."[24]

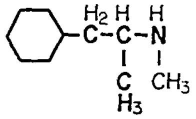
It has long been known that anorexia follows the use of ephedrine.[25] However, since the drug has been used mainly for other purposes, the loss of appetite, along with anxiety and insomnia, has been considered an untoward effect of this drug. It is of interest here because it emphasizes the invariable association of diminution of eating with central stimulation in the entire series of drugs.[26] With the introduction of amphetamine (Benzedrine) sulfate, however, the development of a potent cephalotropic action made its use in the treatment of obesity feasible.[27] The sulfate and phosphate of levo-amphetamine (and more recently levo-amphetamine alginate [Levonor]), amphetamine resin complex (Biphetamine Resin), dextro-amphetamine (Dexedrine), methamphetamine (Amphedroxyn, Desoxyephedrine, Desoxyn, Desyphed, Dexoval, Doxyfed, Drinalfa, Efroxine, Methamphetamine, Norodin, Semoxydrine, Syndrox) hydrochloride, phenylpropanolamine (Propadrine), phenmetrazine (Preludin), phenyl-*tert.*-butylamine resin (Ionamin), and diethylpropion (Tenuate, Tepanil) hydrochloride also belong to the series. However, (as if amphetamine were somehow loathsome) manufacturers of the newer amphetamine congeners tend to avoid and even to disclaim in promotional literature that there is any connection between their compound and amphetamine. The lack of similarity among the so-called generic names designated for these newer amphetamine congeners is worthy of note. Yet it is a simple matter to demonstrate their close chemical and pharmacological relationship. As can be seen in the structural formulas of these agents in the figure, they differ very little from one another, and, as indicated by the heavy lines and lettering, there is a configuration common to them which apparently confers the cephalotropic action.[27b] Thus, they are all amphetamine congeners, and, since amphetamine is so well understood and well established, it seems appropriate to use it as a reference standard.

Whereas it is probable that the structural differences between members of the amphetamine series makes one or the other a more or less potent cephalotropic drug than is amphetamine, it is also probable (no evidence to the contrary) that the so-called anorectic effect is the direct consequence of the central stimulant action common to all.[27b] From the accumulated experience, it seems unlikely that any minor structural change in this group which continues the same theme will separate the effect on appetite from the other effects of the central stimulant action that may be clinically undesirable. Yet it is precisely this which is inferred from many claims made for these drugs, namely, the recurrent claims for reduced incidence of insomnia, anxiety, and nervousness, with potent anorectic effect.

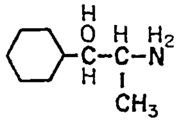
Ephedrine



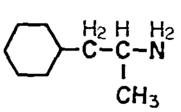
Methamphetamine, Desoxy-ephedrine



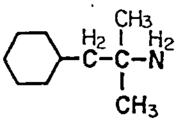
Phenylpropanolamine (Propadrine)



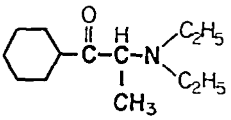
Amphetamine (Benzedrine)



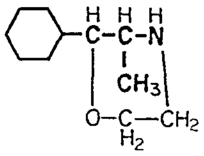
Phenyl-*tert.*-butylamine resin (Ionamin)



Diethylpropion (Tenuate, Tepanil)



Phenmetrazine (Preludin)



Although deaths have occurred from the amphetamine drugs, relatively few cases of acute poisoning and serious reactions have been reported as a result of their present large-scale and continued use. They are not innocuous, however. Since they tend to induce insomnia, it is not surprising that the amphetamine drugs are of no value for the night-eating syndrome. They also may cause restlessness, excitement, depression, irritability, exhaustion, headache, dizziness, halitosis, dryness of mouth, burning in the throat, heartburn, nausea, vomiting, and diarrhea.[28]

The typical sympathomimetic effects on the cardiovascular system, more developed in some members of this group than in others, provide a special area of potential danger. A rise in blood pressure, increase in cardiac work and heart rate, or the development of cardiac arrhythmias may be to be used in patients with heart disease.[11] Reports of good results with sodium liothyronine (Cytomel) in obesity have recently appeared.[45] Small doses which did not disturb metabolic function, cholesterol levels, blood pressure, and heart rate were used. Central stimulation as evidenced by nervousness or tremors was not noted. It should be pointed out, however, that the effect of liothyronine per se was not examined—rather its influence on a regimen, which also included amphetamine and amobarbital (Amytal), was examined. None of these results, therefore, applies to the liothyronine alone. Further examination is warranted.

Sedatives and Tranquilizers.—Since an emotional disturbance of some sort is the basis of overeating in many persons, sedation and tranquilization may possibly assist in depression of appetite. The effect of chlorpromazine (Thorazine) on overeating has been reported to be effective in some cases. Unfortunately, the study was poorly controlled,[46] and the necessary confirmation has not been forthcoming. It is possible that this form of medicament will be effective for the night-eating syndrome—a situation in which the stimulant action of amphetamine is likely to make matters worse. Mixtures of an amphetamine material with a barbiturate or a tranquilizer, such as amobarbital, rauwolfia (Raudixin, Rauserpa, Rauval), or meprobamate (Equanil, Meprospan, Meprotabs, Miltown) to counteract the undesirable central stimulant effects of the amphetamine drugs, have been tried and reported to be both effective and useful.[47] Better studies are necessary to confirm the usefulness of the combination.

Bulk Producers.—Bulk has long been suggested as a means of satiating the appetite of the obese. Unfortunately, cabbage, lettuce, and other articles of the typical grassy, high-bulk, low-calorie diet do not appeal to the average overeater who perversely prefers to distend his stomach with undiluted fat, protein, and carbohydrate. Cellulose and similar materials have been suggested as a substitute for food, but, since this provides bulk for the intestine as well as for the stomach, in the amounts necessary to stay gastric activity, it could never be a satisfactory substitute for food. With these limitations in mind, it is no surprise that methylcellulose has been found neither to appeal to nor to stay the appetite of the average person who overeats. The physiological basis for this is very nicely explained in experiments by Miller.[30]

Purgatives and Diuretics.—Many expensive obesity cures and regimens depend on an exhibition of weight loss to entice the patients into continuing treatments, especially in expensive salons. In order to induce gullible persons to a course of treatments, devices are used which provide spurious evidence of prompt effectiveness, without a difficult dietary regimen. Cathartics, diuretics, and salt restriction are often used in such schemes, for, through dehydration, they induce some weight loss very promptly. In contrast to the effect in the edematous patient, however, in the obese patient, weight loss by water excretion is both meaningless and senseless. Through the operation of the normal homeostatic mechanisms, the moment an opportunity arises to retain electrolyte and the water it binds through osmotic tension, the lost water is retained, and, with it, the lost weight is regained. In any event, it does not represent a loss of fat.[48]

Miscellaneous Devices.—Although there is no reason to think that vitamins and minerals would have any merit, it is not at all surprising that they should be recommended for use in the treatment of obesity (since they have been tried for virtually everything else). What is strange, however, is that sweets (Ayds, R.D.X.), containing other nutritional elements in addition, should have been introduced and should have their enthusiastic supporters. Weight loss through the use of such unscientific preparations can only be excellent proof of the importance of the psychogenic elements involved and of the effectiveness of suggestive advertising.

Summary

New and logical pharmacotherapy for persons who overeat will more likely come with understanding of the processes involved than through the current practice of developing more variations on old themes which have already been well exploited and have not satisfied the need. There is really nothing new on the scene. There are no "anorexiants" to fit specific disturbances in eating patterns, and there are no useful depressants of the appetite center, wherever it may be. Total therapy must consider the psychosocial aspects of eating patterns and the desire to lose weight, as well as the specific psychological or physiological disturbance which has brought on the hyperphagia. In virtually every instance, motivation for losing weight as well as the psychological reasons for overeating are important considerations in determining the therapeutic regimens which are likely to be effective and to lead to sustained benefits.[49] Current pharmacotherapy for persons who overeat has limited use. Insofar as drugs are concerned, at the very best, their potential is secondary to the elimination of the cause of the hyperphagia. Drugs which give assistance along the lines now available provide short-lived symptomatic relief only. These seem to be useful only as adjuvants to a carefully controlled diet and, in many cases, some sort of psychotherapy.

NOTE: References for this article are available in reprints.

CLINICAL SCIENCE

DETERMINATION OF BENCE JONES PROTEIN IN THE URINE

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Although the introduction of electrophoretic methods has led to a much improved characterization of the abnormal globulins which occur in patients with multiple myeloma, the simple determination of the presence of Bence Jones protein in the urine has remained as important as ever for the diagnosis of multiple myeloma. This remarkable thermolabile protein, with a molecular weight of 44.000, is present in 50 to 60% of patients with myeloma. Bence Jones protein must be distinguished from the myeloma globulins, with a molecular weight of 160.000 or greater, that are present in the serum. Irrespective of electrophoretic criteria, the diagnosis of Bence Jones protein in the urine must be accepted if a protein is present which precipitates between 45 and 60 C (113 and 140 F) and dissolves again between 90 and 95 C (194 and 203 F).

In our experience, the presence of Bence Jones protein proves the diagnosis of multiple myeloma. We have never seen an exception to this rule, although the literature mentions that Bence Jones proteinuria has been found in patients with lymphatic leukemia and bone diseases other than myeloma. The statement that Bence Jones proteinuria occurs in patients with lymphatic leukemia should be taken with a grain of salt. The actual reports of such cases are mostly found in the older literature and are merely repeated in the modern textbooks. These observations were made at a time when sternal marrow puncture was hardly ever performed. In the years gone by, many cases of plasma cell leukemia, that is, multiple myeloma with an invasion of the plasmoblasts into the peripheral blood, have been diagnosed as lymphatic leukemia. This error is sometimes difficult to avoid, because the myeloma cells, after invading the blood stream, often change their appearance and resemble lymphocytes more than myeloma cells. In the near future lymphatic leukemia will only rarely be confused with plasma cell leukemia, because a bone marrow puncture will immediately reveal the true character of the disease. Bence Jones proteinuria has allegedly been found in patients with different bone diseases. In most of these cases, however, the abnormal protein did not have both characteristics which must be present before the diagnosis of Bence Jones proteinuria can be made.

It will hardly be necessary to add that, although Bence Jones proteinuria is a pathognomonic sign of multiple myeloma, the reverse is not true. Therefore, in the absence of Bence Jones proteinuria the search for other manifestations of myeloma must be continued.

Determination of Bence Jones Protein

In most clinical laboratories there is much confusion about the methods which must be used to demonstrate the presence of Bence Jones protein in the urine. Consequently, erroneous laboratory results reporting Bence Jones protein as "albumin" often lead to fallacious diagnoses.[1] In view of the diagnostic importance of Bence Jones proteinuria, it seems worthwhile to describe the methods which we have found to be reliable.

Rules.—Jacobson and Milner[2] have laid down most of the rules which must be followed for a correct execution of the test for Bence Jones protein: 1. The urine to be tested should be fresh, unless the specimen has been frozen. 2. The urine should be centrifuged before the testing is started. 3. The precipitation between 45 and 60 C (113 to 140 F) should be done at a pH of about 5.0. 4. The solution of the Bence Jones protein at the boiling point should be tested at a much lower pH, i. e., 2 to 3. This pH results if, as recommended by Magnus-Levy,[3] an equal amount of 5% sulfosalicylic acid is added to the urine. 5. Bence Jones protein dissolves at boiling only if the amount of protein is not excessive. 6. Filtration of the urine before or after boiling should be avoided. Precipitates should be collected by centrifugation.

Method.—The three major steps of the method are as follows: 1. When addition of sulfosalicylic acid solution to urine does not cause a precipitate, no Bence Jones protein is present in the native urine. 2. If a precipitate forms in the urine after addition of sulfosalicylic acid solution, the search for Bence Jones protein must be continued. 3. Before the test the pH of the centrifuged urine should be examined with sodium dinitrophenylazo-

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From the Department of Medicine of Beth-El Hospital.

naphtol disulfonate (Nitrazine) paper. If the pH exceeds 5, the reaction should be adjusted with 2% acetic acid. The urine is then heated to 60 C (140 F), if possible in a water bath. In the presence of Bence Jones protein a precipitate will occur. After the tube has been kept for one minute at 60 C, equal amounts of sulfosalicylic acid are added. This will often cause the formation of much heavier precipitate, because only part of the Bence Jones protein will be precipitated if the urine is kept at 60 C during one minute. (*a*) If, after this addition of sulfosalicylic acid, the turbidity does not exceed a 2+ protein reaction, the test tube can be boiled over a free flame. The precipitate then will dissolve and return after cooling. (*b*) If, after the addition of sulfosalicylic acid, the ensuing precipitate is unusually heavy, the turbid fluid must be diluted with normal urine until the precipitate amounts to a two + protein reaction. An aliquot of this diluted specimen is boiled over a free flame. The precipitate will dissolve and return after cooling. Sometimes it will be necessary to add several drops of sulfosalicylic acid to the diluted specimen before boiling to restore the pH of 3.

This simple demonstration of Bence Jones protein in the urine, which every physician can perform in his office, has more than held its own as a major diagnostic feature, notwithstanding the progress obtained by the introduction of modern complicated laboratory methods.

Clarification

Possible Misinterpretation of Test.—Many authors are of the opinion that in patients with multiple myeloma Bence Jones proteinuria is usually combined with albuminuria.[4] Van Dommelen,[5] in an excellent thesis, reported that among 541 myeloma cases collected from the literature, 34% of patients had Bence Jones proteinuria only, 6.3% Bence Jones proteinuria plus albuminuria, 25.5% albuminuria alone, and 25% no proteinuria. Van Dommelen himself found Bence Jones proteinuria in 50% of 36 patients with myeloma and albuminuria in 17%. He never encountered the combination of Bence Jones proteinuria with albuminuria. Magnus-Levy[6] and Osgood and Haskins[7] have emphasized that simultaneous excretion of Bence Jones protein and albumin occurs only rarely. This seems at variance with the data in the modern literature which emphasize that electrophoretic examination of the urine frequently reveals the presence of both albumin and a myeloma globulin in the urine.

The excellent study of Osserman and Lawlor[8] may be mentioned as an example. They report that, in at least some of their cases of multiple myeloma, electrophoresis of urine containing myeloma protein revealed the additional presence of other proteins—mainly relatively small amounts of albumin. This discrepancy can be partly explained because, in these cases, the possibility of a complicating pyelonephritis was not especially considered (see below). In addition, the electrophoretic examination of the proteins of the urine is customarily performed only after the urine has been concentrated by dialysis against a 30% watery polyvinyl-pyrolidone solution or against a 15% watery carboxymethylcellulose solution. When such a dialysis is continued for three or four days, the urine can be concentrated 150 times. Usually the dialysis is continued until the urine contains 1.5 to 2% protein. It is evident that electrophoresis of the dialyzed and concentrated urine may reveal the presence of minuscule quantities of albumin and globulin which cannot be demonstrated during the examination of the native urine for Bence Jones protein.

Wolvius[4] found that 93% of the protein present in the urine of a myeloma patient consisted of gamma globulin and 3% of albumin. Since the total protein content of this urine amounted to 3 Gm. per liter, the albumin content of the native urine must have been 0.009%. In two other urines containing Bence Jones protein, the same author found about 0.005 and 0.002%, respectively, of albumin. These quantities are far less than the "faint trace" which the laboratory so often finds in a native normal urine. In this way it can be understood that, although other proteins can be discovered electrophoretically in concentrated Bence Jones protein-containing urine, at best only a trace of albumin or globulin is found if the tests for Bence Jones protein are performed in native urine.

It has been pointed out that, in case the Bence Jones protein content of the urine is large, the test mentioned above will not always completely exclude the presence of albumin. When the addition of sulfosalicylic acid causes a heavy precipitate, the thick suspension must be diluted with normal urine. It is possible that, due to this addition of normal urine, a significant amount of albumin, for instance 0.1%, could be so much diluted that boiling would no longer form a visible precipitate.

Modification of Test.—The possible error mentioned above can be avoided by the following modification of the test: Adjust the reaction of the urine containing Bence Jones protein to a pH of 5 and heat for one minute at 60 C (140 F), then centrifuge. Save the precipitate, heat the supernatant at 60 C, and repeat both the collection of the precipitate by centrifugation and the heating of the supernatant to 60 C, until at 60 C no further precipitate forms. If much Bence Jones protein is present, it will be necessary to repeat the precipitation at 60 C and subsequent centrifugation five or six times. As soon as no further precipitate forms at 60 C, all the Bence Jones protein must have been removed. It will then be seen that addition of sulfosalicylic acid to the supernatant will cause, at the most, a faint precipitate. All the protein precipitates which have been formed at 60 C are then collected and suspended in so much normal urine that addition of an equal amount of sulfosalicylic acid causes a 2+ protein reaction. This suspension will clear at boiling. It follows that all, or practically all, of the protein present in the urine is Bence Jones protein, because it is precipitated in its entirety at 60 C and practically all the protein precipitated at 60 C dissolves at boiling.

Only the slight turbidity which is commonly caused by addition of sulfosalicylic acid to the last supernatant which has remained clear after heating to 60 C could be due to a protein other than Bence Jones protein. Even this turbidity does not indicate the presence of albumin, because during boiling the solution clears completely. This slight turbidity may represent a trace of a proteose, *i. e.*, a protein which does not precipitate at 60 C but dissolves at boiling. In addition, the possibility that even after repeated heating to 60 C a trace of Bence Jones protein remains in colloidal solution must be considered.

This slightly more complicated test shows once more that in patients with multiple myeloma without complications only Bence Jones protein and no albumin is eliminated in the native urine.

Comment

Part of the difference of opinion about the rarity or frequency of the combination of albuminuria and Bence Jones proteinuria can be explained, because the aforementioned conclusions hold true only for cases of myeloma without complications. Since the abnormal gamma globulin of patients with myeloma does not protect the victim against infections, febrile diseases, such as bronchitis, pneumonia, tuberculosis, meningitis, and especially pyelonephritis are frequent complications. In myeloma patients who are suffering from fever or pyelonephritis, Bence Jones proteinuria may be complicated by albuminuria. The same may happen in the rare cases in which the myeloma patient had been suffering from a chronic glomerulonephritis before the myelomatous disease developed.

In such cases the Bence Jones protein must be separated from the albumin. As in the original test, the native urine is first centrifuged to remove the white blood cells and other formed elements and the supernatant is brought to a pH of 5 and kept at 60 C (140 F), for one minute. The turbid solution is then centrifuged, and the supernatant which contains the albumin fraction is discarded. The precipitate is suspended in normal urine, and an equal amount of sulfosalicylic acid is added. In the case of a heavy precipitate, the mixture must be diluted with normal urine until the turbidity resembles a two + protein precipitation. An aliquot of this turbid solution is mixed with a few drops of 5% sulfosalicylic acid. The turbidity will disappear at the boiling point, which proves the presence of Bence Jones protein. In this way the presence of the latter protein can be proved if in the same urine albumin is present.

Summary

The presence of Bence Jones proteinuria is pathognomonic for multiple myeloma. If addition of sulfosalicylic acid to urine does not cause a precipitate, no Bence Jones proteinuria can be present.

The presence of Bence Jones protein can be demonstrated by heating fresh urine at a pH of 5 to 60 C (140 F). If a precipitate forms, equal amounts of sulfosalicylic acid are added. If the turbidity caused by the ensuing precipitation does not exceed a 2+ protein reaction, the urine can be brought to a boil, and the precipitate will disappear. In case the turbidity caused by the addition of sulfosalicylic acid is unusually heavy, an appropriate amount of normal urine should be added before the urine is boiled.

In patients with multiple myeloma without complications only Bence Jones protein but no albumin is eliminated in the native urine. The frequently occurring febrile complications, especially pyelonephritis, however, could be the reason why a patient with Bence Jones proteinuria could also eliminate an appreciable quantity of albumin in the native urine.

Linden Boulevard and Rockaway Parkway (12) (Dr. Snapper).

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THE JOURNAL
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POSTOPERATIVE SEPSIS

INTEREST in the medical literature and lay press concerning infections contracted in hospitals has attained major proportions. The lay press has produced a distorted echo of the medical reports, and these noisy repercussions have left the public with the unwarranted impression that hospital wards today are increasingly congested with patients suffering septic complications caused by inadequate techniques and inappropriate use of antibiotics. Case reports and investigations tracking down postoperative sepsis appear in an endless series and commonly read like a miniature detective story, in which the bacteriologist, in the role of a clinical Sherlock Holmes with culture tube and notebook in hand, hunts for the break in hospital technique.

In contrast to his counterpart in criminal law, the bacteriologist must let his case rest solely on circumstantial evidence. A synopsis of a mock case incriminating hospital technique as responsible for postoperative sepsis would read as follows. Some patients develop infections postoperatively, and the same species of bacteria can be cultured from a laundry shoot or from a furuncle on the thigh of a ward helper. Therefore, the laundry shoot or ward helper caused the septic complication. This is guilt by association. An impartial judge would ask what type of patient became infected (Was he debilitated? Was his immune mechanism intact?), how severe was the infection (What indexes are there to evaluate the severity of a postoperative infection?), was the patient himself the source (Was he, in accord with the interpretation of Rene Dubos,[1] a thriving example of symbiosis which illness and hospitalization converted to a septic complication?), was surgical technique optimum (Did a hematoma or local tissue necrosis favor the primary lodgment and growth of a few skin bacteria?), and when are environmental bacteria a cause and when a result of a septic complication?

These considerations and many others illustrate two basic problems yet to be solved in the interpretation of postoperative sepsis. The first and most important is the definition. Reports in the current surgical literature commonly do not define surgical sepsis. Thus, it is patently impossible to compare reports from different institutions or to evaluate trends in rates of sepsis. The second basic problem is our limited understanding of the pathogenesis of postoperative sepsis. Our estimation of the relative importance of patient resistance, surgical technique, bacterial virulence, minimum dose of bacteria needed to produce a complication, and other factors is clouded by our basic ignorance of wound healing. At present, doubtless because of a legacy from the past when environmental bacteria were unquestionably the major source of infection in surgical incisions, attention has been directed to improving the bacterial environment of the surgical patient. There is obvious value in these measures reducing the bacterial population, but their ultimate value will be reappraised when we can answer this basic question: "What are the conditions that permit the few bacteria present in most clean incisions to produce the occasional septic complication?"

Although we do not have an acceptable and universal definition of postoperative sepsis or a full explanation of the appearance of most septic complications, there is merit in the efforts of many hospitals today to document the incidence of sepsis on surgical services. These studies at least map out the dimensions of the problem and allow us to see in general terms what the record has been in the past. Of the numerous reports that may be mentioned, those by a group working at the Massachusetts General Hospital have added a new approach which may prove to be significant for future studies. These reports,[2] one of which appears on page 1068 in this issue, have estimated the incidence of postoperative surgical sepsis over a 27-year period by reviewing three standard operative procedures. By focusing on a single operation to evaluate trends in postoperative sepsis rates, the irrelevant variations caused by the inclusion of different types of operations in different years are avoided. This appears to be a distinct advance over studies that have bulked together various operations with clearly diversified risks of sepsis. A drawback to these retrospective studies is the incompleteness of the bacteriological data from years when bacteriophage typing of staphylococci, available today, was lacking.

As a rebuttal to the current criticisms stating that the risk of postoperative infection is increasing, it is noteworthy that these reports do not find any evidence for an increase in the incidence of surgical sepsis after herniorrhaphies and hysterectomies over a 21-year period. In fact in only one division of the hospital was an increase in sepsis noted after the operations studied. This occurred over the past five years after subtotal gastrectomies, at a time when more emergency operations for acute, massive bleeding were performed. If future studies from other institutions are in accord with these facts, it may be concluded that any rise in the risk of postoperative surgical sepsis is more apparent than real and that such impressions are based on the treatment of more debilitated patients by a greater variety of complex technical procedures.

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THE UNHAPPY FAT MAN

Many unrelated forces perversely contribute to making one type of human configuration desirable when its opposite is more likely. Thus, corpulence was the symbol of affluence and virility when the masses were undernourished, whereas today, when food is much more abundant, obesity is more commonly associated with those who eat potatoes because they cannot afford filet mignon. Although our culture applauds the slim trim figure, it is openly proclaimed by many that the curvaceous classic female form has desirable voluptuous qualities. The "Man of Distinction" is never a fat man, yet business customs make the restaurant with rich food and too much drink the appropriate place for the big business deal. In this age of anxiety, the well-known euphoria that comes from a full stomach has to contend with the fear that obesity is associated with atherosclerosis and a shortened life. Surprisingly enough, therefore, one has only to turn to the advertising pages of any medical journal to find the solution to these conflicts promised in a contemporary simple.

In another section of this issue, the Status and Prospect of Drugs for Overeating is explored in a report to the Council on Drugs. It points out that the problem is not merely that of depressing appetite; since the causes are diverse, the treatments cannot all fit into a single regimen. Probably less than 10% of all cases are due to genetic, glandular, physiological, or physical abnormalities; in the others, the obesity is not related to defects which disturb the physiological appetite mechanism at all. The overeating is compulsive, not stayed by amounts of food which would satisfy an appetite drive related to metabolic or homeostatic mechanisms, and is most likely the consequence of psychological disturbances in which the ingestion of food provides a source of deep psychic satisfaction. Because of this, the approach to obesity on the basis of caloric intake and caloric need avoids critical issues.

Of course, obesity will respond to any measure which effectively restricts the amount of food consumed. It has been shown that the treatment of obesity is misleadingly successful in the early stages, but the final results are discouragingly poor. Only 2% of one group entering a course of treatment maintained a significant weight loss for as long as two years. Compounding this high level of eventual failure is a high incidence of serious psychic disturbances during the course of treatment as the result of deprivation of psychic satisfactions supplied by hyperphagia.

The report points out that, in most cases, drug therapy of obesity is impotent against the disturbances which stimulate the overeating. Thus, the large group of drugs which are commonly called anorexiants do not depress the abnormal appetite drive directly but rather distract the patient by central stimulation. Consequently, the weight lost by the obese through the use of drugs is usually regained soon after therapy is stopped. It is also pointed out that there is a strong family resemblance between members of this group of drugs with few, if any, important pharmacological, hence therapeutic, differences.

The report concludes that the current pharmacotherapy has limited use for the obese and that, at the most, it is secondary to the elimination of the cause of hyperphagia. This brings the rational therapy of obesity down to the same plane as that of all other medical syndromes in which effective therapy requires an understanding of, as well as an attack against, the causes of the disturbance.

RECENT STUDIES OF THE ANATOMY OF THE LUNGS

The story of the bronchial tree begins with Aeby, who in 1880 published his "Der Bronchialbaum des Menschen, und der Thiere." The work dealt with 48 species belonging to some 14 mammalian families. Aeby concluded that "the ground plan of the bronchial tree is the same for all animals" and that "each lung possesses a dominant axial structure to be called the stem bronchus." He emphasized the monopodial character of the major branches and the monopodial character of the blood vessels. Aeby emphasized the relationship of bronchi to the main pulmonary arteries in distinguishing an eparterial from a hyparterial group. A major part of his monograph was devoted to the anatomy of the bronchial tree in man.

The English pathologist Ewart contributed, a few years earlier, a detailed study of the distribution of the bronchi and pulmonary vessels in a large number of lungs in man. "Moreover, a suspicion had arisen in my mind," he states, "that the present deficiencies in our anatomical knowledge might perhaps be held responsible for the halting and spasmodic feature in the development of pulmonary surgery, contrasting with the steady progress made in the surgery of other regions." Ewart's concept of the "respiratory districts" in animals is fundamentally the same as the modern view of the bronchopulmonary segments. Narath extended Aeby's

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1. Bloomer, W. E.; Liebow, A. A.; and Hales, M. R.: Surgical Anatomy of the Bronchovascular Segments, Springfield, Ill., Charles C Thomas, Publisher, 1960.

observations on the bronchial tree in mammalia in an illustrated monograph based on prepared casts of the bronchial trees and vessels. Huntington reemphasized the fact that "Aeby was the first to recognize the existence of the eparterial bronchus and its morphological significance in the intrapulmonary architecture."

Further contributions to our knowledge of the anatomy of the lung were made by the embryologist von Baer, by Kölliker, and by His. His demonstrated the asymmetry of the bronchial tree and maintained that monopodial and dichotomous systems are not necessarily exclusive. Kramer and Glass, in 1932, produced an accurate diagram of the bronchial tree, and introduced the term, "bronchopulmonary segment." This corresponded to Ewart's concept of "respiratory districts." In 1943, Chevalier Jackson and Huber published a nomenclature that has been widely accepted and that has served as the basis for the terminology used by Boyden and his co-workers, and in the recent volume by Bloomer, Liebow, and Hales.

The introduction of lipiodol into bronchography in 1922 by Sicard and Forestier stimulated interest in the practical anatomy of the lungs. In 1955 Boyden and his co-workers published their systematic and detailed researches on the anatomy of the lung. The volume is the result of meticulous dissection and study carried on for a decade. Their book contains a detailed and practical nomenclature that serves as a key to the analysis and recording of the variations in the patterns of arrangement of the bronchi and vessels.

The most recent contribution to the subject is a volume entitled "Surgical Anatomy of the Bronchovascular Segments" by Bloomer, Liebow, and Hales.[1] These authors followed the nomenclature and tabulations of Boyden in order to permit a detailed comparison of their observations with his.

The art of preparing anatomical casts by the intravascular injection of solidifying media goes back to Swammerdam in Holland in 1670 and to his pupil Ruysch. The method of injection and corrosion has been used for many years. Aeby and Ewart made use of it. Narath made some 600 casts of lungs from 133 different species, including 33 from man. Huntington, at Columbia University, prepared a collection of specimens injected with wax.

The authors of "Surgical Anatomy of the Bronchovascular Segments" employed the method of casting of the bronchi and vessels in vinylite plastic. The casts have been maintained as a permanent collection. The book was especially designed to serve as a guide to the dissection of the bronchovascular segments. The advantage of the casts is that they lend themselves to stereoscopic reproduction, as in the supplement to their book. This supplement consists of 168 stereoscopic transparencies designed to match exactly the black and white illustrations in this book.

THE PHYSICIAN'S WRITING AND READING

Dr. Henry E. Sigerist, noted medical historian, was unabashed in his confession of the mental travail that precedes the preparation of a lecture or a manuscript. An enchanting teacher as well as an incisive lecturer in great demand, Sigerist entered into the preparation of either a spoken or a written text with great reluctance. At times emotional concern was precipitated by thoughts that preceded the preparation of a lecture to students, young or mature.

When Sigerist had committed himself to the preparation of a manuscript, it was necessary that he feel "pregnant" with the subject for a time. The material was on his conscience day and night. The next step was a procedure used by Emile Zola and Guy de Maupassant. A short outline, not longer than a single page, was prepared as the preliminary step in composition. With the arrival of the fatal morning for the word-by-word and line-by-line implementation of the outline, a definite number of pages were assigned for the day's activities. These were prepared in longhand. The goal did not exceed five pages per day between the hours of 9 and 12 in the morning. The rest of the day was devoted to reading, research, and correction of previously prepared copy.

"I know it is generally recommended that scientific papers be as short and as factual as possible. As a result they are informative, to be sure, but make frightfully dull reading. I know of famous medical journals in which every article is edited or even rewritten entirely by a highly competent staff of elderly ladies according to set standards, and the result is that every article reads as if it had been written by the same person. This is just fatal. No two individuals are alike, and no matter how factual an article is, we wish to get a grasp of the personality behind it. I said that the prerequisites of good writing are clear thinking and command of the language in which you are writing. The latter is a sore spot, particularly in America. We should expect that a medical student has acquired a thorough knowledge of English in college. Some have, but very many have not. I was foreign born, and it was necessary that I improve my language from the first day on and I am still doing it today, after twenty-two years.

"My method is very simple and I can recommend it. It consists of reading good writers critically. When I first came to America I read a number of novels critically, a few pages a day only, analyzing the sentences and making notes of words that I would not have used, but that struck me as being very expressive. I also made notes of entire sentences, and in this way, in a couple of years, I increased my vocabulary and improved my syntax considerably. I still follow the practice."

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Sigerist has some sound advice on what the doctor should read—nonprofessional reading, that is. Nonmedical reading is recommended for cultural benefit to avoid the waste of treasured time. Time is too precious to be squandered. Nonprofessional reading should not be restrictive. What is good reading for a lawyer or a banker should be good reading for a physician. Sigerist's day began with the reading of a short poem. It will be necessary to set the alarm a few minutes earlier if this habit is acquired by other physicians. Not more than 30 minutes a day were devoted to newspapers and current newsworthy periodicals. Before taking up light literature, however, 50 pages of a worthwhile book were read perceptively. Sigerist did not consider it necessary to read only new books. "Any good book written during the last 5,000 years seems to qualify." His essay on the physician's writing and reading, as well as a number of others, has been published recently in a volume, "On the History of Medicine."[1] The essays selected are not pedantic. They were written with ease and grace and selected with discrimination for re-publication.

BENCE JONES PROTEIN IN THE URINE

In 1845, Bence Jones observed a heavy precipitate form when he boiled the urine of a patient suffering from softening and brittleness of the bones. To his surprise, the precipitate completely dissolved after the addition of nitric acid, then returned when the urine was cooled, and when boiled again, it reliquefied.[1]

This remarkable protein has since been studied by numerous investigators. As defined today, Bence Jones protein precipitates at a temperature between 45 and 60 C and dissolves at 100 C. The Danish investigators, Effersøe and Tidstrøm, published a salt precipitation test,[2] in which each of two samples of urine from a patient with myeloma is mixed with a different amount of 3.5 M potassium phosphate solution until, in one tube, a 70% concentration of potassium phosphate is produced, whereas, in the other tube, a 90% concentration is present. If a heavier precipitate occurs in the first tube than in the second, the presence of Bence Jones protein is practically proved.

Precipitins against Bence Jones protein may be prepared simply by injecting rabbits with this protein. However, the serological demonstration of Bence Jones protein had become practically obsolete until it was revived by Collier and Jackson.[3] Electrophoretic analysis of protein-containing urine of myeloma patients will reveal the presence of an abnormal globulin as a sharp peak in the electrophoretic pattern. Although such an abnormal myeloma globulin may be important diagnostically, it is not necessarily a Bence Jones protein. Part of these myeloma globulins excreted in the urine will not precipitate at 40 C and dissolve again at 100 C. Yeoman[4] has reported that staining with methyl green and pyronin reveals a deep red stain of the electrophoretic protein band, which contains the Bence Jones protein. This might indicate the presence of large amounts of ribose nucleic acid.

There is today a tendency to circumvent the determination of Bence Jones protein by heat precipitation. The Danish authors say that the different pH requirements, which are mandatory to determine correctly the precipitation at 40 to 60 C and the disappearance of the precipitate at boiling, make this classical test laborious. Yeoman complains about the shortcomings of the heating and salt precipitation tests. A new method of heat precipitation of Bence Jones protein is described in this issue, page 1137. Although the authors say that Bence Jones protein occurs only in multiple myeloma, and occasionally, in lymphomatous diseases, a protein may be present in the urine which could be easily confused with Bence Jones protein. Such a protein may be precipitated at 40 to 60 C but will dissolve between 75 and 80 C. In other cases, a trace of protein may come down at 65 C but usually only after the urine has been kept at this temperature for 15 minutes. This precipitate may dissolve at a higher temperature. These are not true Bence Jones proteins, and errors may result, unless this examination is performed by competent investigators.

The custom now is to accept that, in urine which contains Bence Jones protein, albumin usually and other proteins occasionally are also present. This varies with the opinion of Magnus Levy who declared that the better the chemist, the less albumin he will find in urine which contains Bence Jones protein. The difference of opinion can be explained. After urine with Bence Jones protein has been concentrated 10 to 100 times, as is necessary before the electrophoretic pattern is made, minute traces of albumin (or globulin) present in the native urine may appear in the electrophoretic curve. However, these minimal traces of albumin or globulin cannot be detected in the native, nonconcentrated urine with current laboratory methods. A concomitant pyelonephritis may be the reason that, in urine from a patient with myeloma, moderate amounts of albumin may be found in the presence of Bence Jones protein. The method published in this issue, it is believed, will go far to restore heat precipitation as the clinical method of choice for determination of Bence Jones protein.

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ORGANIZATION SECTION

"LIFE THROUGH MEDICINE"

The General Scientific sessions of the 109th Annual Meeting at Miami Beach emphasized the newer advances in medicine with the program theme "Life Through Medicine."

In addition to a multitude of scientific papers, the meeting featured 290 scientific exhibits plus a daily schedule of motion picture and color television programs. Fresh pathological specimens were demonstrated by outstanding pathologists throughout the nation. Another perennial favorite at the convention hall was the physical examination for physicians attending the meeting, including, for selected subjects, the "Two-Step Test" developed by Dr. Arthur M. Master.

Warns Against Popular Food Fads

Too often the suspicion of anemia prompts the administration of vitamins without consideration of diagnosis or of the usefulness of these therapeutic agents, Dr. Richard C. Vilter, told the opening general scientific session. Dr. Vilter, director of the department of internal medicine at Cincinnati General Hospital, and recipient of the 1960 Joseph Goldberger Award, said that although dietary deficiency is a common cause of anemia, the prescription of a mixture of essential nutrients is by no means a panacea for anemia, and much precious time may be wasted through fruitless vitamin therapy. Yet, through the medium of often repeated and deftly worded advertising, Dr. Vilter added, the public has come to believe that the surest way of "re-energizing" blood is to take a vitamin-mineral mixture, and many physicians tend to take this short cut in lieu of time-consuming diagnosis.

This might be reasonable if vitamin deficiencies constituted a major cause of anemia in the United States. Such is not the case, he said.

Statistics compiled at Cincinnati General Hospital over the past three years showed that only about 4% of the anemic patients were ill because of vitamin deficiency, compared to 18% who had blood-loss iron deficiency. The figures, said Dr Vilter, do not support the common practice of "shotgun" vitamin therapy for anemia. When vitamin lack is the cause of anemia, a very specific and dramatic result will be obtained only when the deficient substance is prescribed.

Greatest Help in Diagnosis

When anemia is suspected of having its origin in a deficiency of one of the essential nutrients, simple laboratory procedures offer the greatest help in diagnosis, Dr. Vilter said. The simplest is the microscopic study of the stained blood film. Technical errors may invalidate the volume indexes, but a brief glance at the blood film will settle the question of macrocytosis or microcytosis and of normochromia or hypochromia. Bone marrow examination may be necessary when the answer is not apparent from a study of the blood film.

Although niacin and riboflavin deficiencies have been responsible for anemia in animals, there are no documented examples in man of anemia due to such uncomplicated dietary deficiencies. Thiamine, pantothenic acid, and inositol have not been shown to be necessary for human blood formation.

It should be remembered that excesses of some vitamins, particularly the fat-soluble ones, may be deleterious. One hundred thousand units of vitamin A given for many months may cause thickening of cortical bone or hyperostosis. Vitamin D in excess may cause hypercalcemia, nephrocalcinosis, and anemia or uremia.

B Complex Function

The B complex vitamins were discussed by Dr. Robert E. Shank, Danforth Professor of Preventive Medicine at Washington University School of Medicine, St. Louis. Dr. Shank described the research of the past three decades showing that the vitamins of the B complex function as coenzymes that make energy available for body processes.

Thiamine functions within the body as thiamine pyrophosphate, a coenzyme of carboxylase, an enzyme concerned with decarboxylation and oxidation of pyruvic acid. Accordingly, in induced deficiency in experimental animals and man pyruvic acid accumulates in the blood. The accumulation of pyruvic acid in blood that occurs after carbohydrate loading has afforded a clinical test for thiamine deficiency. Dr. Shank noted also that the quantity of thiamine stored in tissues of the normal human being is small and approximates 25 mg., about 20 times the daily requirement for the vitamin. The body has no capacity for storage of additional quantities and excess amounts are lost rapidly in the urine. Determination of concentrations in urine afford a measure of recent intake.

In clinical manifestations of beri-beri, in the so-called wet form of the disease, there is edema, cardiac dilatation, and peripheral vasodilation. The disorder still occurs in the United States among patients whose diets have been severely limited by fad or associated disease. Differentiation from other forms of high-output cardiac failure may be difficult, said Dr. Shank, but administration of between 20 and 30 mg. of thiamine daily may be lifesaving.

The "dry" form of beri-beri is predominantly a polyneuropathy of nutritional origin. Manifestations include muscle weakness, hyperesthesia, loss of

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Note: Many of the papers presented at the Miami Beach meeting will be published in future issues of The Journal *of the American Medical Association* and the A. M. A. specialty journals.

position and vibration sense, and loss of tendon reflexes. In the United States it is noted most frequently in chronic alcoholics and occurs on rare occasions in pregnant women who have had persistent and prolonged vomiting. It would be presumptuous to deduce that the neurological manifestations of this disorder result from a single nutrient deficiency. Response to treatment with thiamine often is disappointing. The most important aspect of therapy is prompt provision of a diet which is adequate in quantity and quality of all essential nutrients.

Another important clinical consideration in relation to thiamine is that diets planned for weight reduction of obese patients are likely to contain inadequate amounts of this vitamin, particularly when the diet provides less than 1,200 calories daily. The human requirement for thiamine is about 0.25 mg. per 1,000 calories, and the national food standard, Recommended Dietary Allowances, proposes that thiamine intakes should not be less than 1.0 mg. per day.

Niacin deficiency, pellagra, is observed mostly in groups who consume relatively large quantities of corn. Corn contains little niacin, and its protein, zein, contributes but small quantities of tryptophane to the diet. Although the possibility remains that corn also possesses a factor which is inhibitory to niacin, this would seem to be but a minor factor in the production of pellagra. An essential consideration in therapy must be the early provision of a diet totally adequate in all nutrients. Diagnosis ordinarily depends on clinical acumen since serum levels of diphosphopyridine nucleotide (DPN) and urinary excretion of metabolic products of niacin are not uniformly reduced in niacin deficiency.

Regarding recent reports attesting to the effect of large doses of niacin (3.0 to 6.0 Gm. daily) in reducing serum cholesterol levels in patients with hypercholesteremia, Dr. Shank said the reduction does not occur uniformly and the mechanism of the action is incompletely explained.

Recent observations show that vitamin B_6, pyridoxine, protects against and is effective in treatment of peripheral neuropathy resulting from isoniazid therapy. About 2% of patients receiving a dose of 300 mg. of isoniazid daily develop neurological abnormalities, while there is an increase to about 40% of patients receiving 20 mg. per kilogram of body weight per day of isoniazid. Patients receiving isoniazid excrete an excess of vitamin B_6 in the urine. Some patients also excrete abnormally large amounts of xanthurenic acid after the administration of tryptophane.

Fat Not an Entity

Dr. Grace A. Goldsmith, Professor of Medicine, Tulane University School of Medicine, told a symposium audience that fat can no longer be considered an entity. Rather it is necessary to think of specific lipid compounds, of which there are many hundreds. Each lipid has a distinct function in the body and many of these functions have not been clarified.

Lipids are carried in the blood attached to protein. One group of lipid-protein complexes—the beta lipoproteins—are suspected of having a role in atherosclerosis. The measurement of cholesterol in blood is only one way of detecting that something may be wrong in fat metabolism. Other more complicated tests have been developed and are giving important information. Actually, normal levels of cholesterol and other serum lipids are not precisely known. It has been suggested that serum cholesterol concentrations of less than 225 mg.% (CQ) may be desirable.

Many factors other than diet influence levels of cholesterol and other lipids in blood. Heredity and hormones are of particular importance. Numerous factors in addition to cholesterol and other serum lipids are thought to be of importance in the cause of atherosclerosis.

To determine the importance of diet and particularly diets rich in highly unsaturated fats in the prevention and treatment of atherosclerosis and coronary heart disease may require 5 to 10 more years of careful study.

Active Acetate

Dr. Robert E. Olson, University of Pittsburgh, told the meeting that the two-carbon fragment, active acetate, is at the crossroads of metabolism because it is an intermediate in the breakdown of practically all of the foodstuffs ingested. Further, it serves as the focal point for diversion of its carbon toward synthetic reactions leading to the manufacture of fatty acids, cholesterol, steroid hormones, and for entry into the Krebs carboxylic acid cycle which leads to the oxidation of the two-carbon fragment to produce carbon dioxide, water, and energy. The full chemical name of the active acetate molecule is acetyl coenzyme A, a derivative which confers on acetate its special reactivity. The coenzyme itself contains the vitamin pantothenic acid plus a cystine derivative which provides a sulfhydryl group which links to the coenzyme.

The physiological disposition of the two-carbon fragment is affected by many factors, including diet, hormonal balance, heredity, and basic enzymatic differentiation of cells. Ketone body synthesis which involves the combination of two two-carbon fragments to yield a four-carbon acid occurs in diabetes. The control of cholesterol biosynthesis in the body, closely associated with the effects of diet on the level of serum cholesterol is also determined in part by the activity of the enzymes which metabolize the two-carbon fragment. Acetylation reactions are also used for the detoxification of drugs.

Wide Range of Subjects

Color television programs ranged from problems of the newborn to problems of aging. A program devoted to Poisoning included a live demonstration of four major types of North American poisonous snakes—rattlesnake, coral snake, copperhead, and cottonmouth—provided by the Miami Serpentarium. Dr. John T. Kilpatrick, Clinical Instructor, University of Miami Department of Surgery, noted that panic causes more damage than the bite of a poisonous snake. The very young and the aged are the most likely victims of snakebite and the intravenous bite is, of course, more dangerous than the intramuscular wound. Standard treatment discussed included cutting fang marks into small crosses, applying suction to wounds, and use of tourniquets.

Many scientific motion pictures, including several "World Premier" showings and film symposia, were offered during the meeting. A premier showing of Disinfection of the Skin, by Dr. Carl Walter, Boston, depicts bacteriology of the skin and, by animation, graphs, and live action, demonstrates disinfection of the hands in a medical setting. Another premier film, Chemical Tests for Intoxication, produced by the A. M. A. in cooperation with the American Bar Association, reviewed the chemical tests for intoxication and the introduction of such tests in court. Also premiered were Physical Diagnosis—Gait and Musculo-Skeletal Disorders, by Dr. William T. Green, Boston; Physical Diagnosis—Communicable Diseases, by Dr. Louis Weinstein, Boston; Disability Decision, produced by the A. M. A., the Department of Health, Education, and Welfare, and the Division of Social Security to explain to medical audiences the kind of evidence needed for the determination of disability; and Emergency Airways—Crisis and Action, by Drs. David S. Ruhe, G. V. Williams, and G. O. Proud, Kansas City. The last film demonstrates the emergency use of the dagger dilator and dagger scissors with the bivalve cannula.

A Medifilm Report of the Miami Beach Annual Meeting was prepared for future release to state and county medical societies, hospitals, and other medical organizations.

Live poliomyelitis vaccines, adolescent nutrition, lung cancer, cardiac massage, health of the migrant worker, and the spread of venereal disease through a New England community were subjects of scientific exhibits. A model prepared by Dr. Max H. Weil, Los Angeles, as a teaching tool and research device showed how shock, heart attacks, or other injuries to the heart affect blood pressure and blood flow. Viewers were able to see and feel the contraction and expansion of plastic vessels as an artificial heart pumped simulated blood through the system.

Radioisotope surface-counting technique as a possible means of predicting susceptibility to heart attacks was explained in an exhibit by Drs. Philip C. Johnson and Gunnar Sevelius, Oklahoma City. The method employs a scintillation counter to monitor the passage of a minute injection of radioactive material through the heart. A rate meter draws tracings similar to those made by an electrocardiograph. The technique has been used to determine myocardial blood flow of patients using medicaments commonly administered for coronary artery disease.

Experience with intrathoracic injury from steering wheels in automobile accidents was illustrated in an exhibit by Drs. William G. Pace, Karl P. Klassen, Charles V. Meckstroth, and William Molnar, of the Ohio State University Health Center, Columbus. A 10-year study of several hundred patients admitted to the University Hospital was outlined and various types of surgical techniques described.

Early use of oxygen in coronary thrombosis was discussed by Dr. A. L. Barach, Columbia University College of Physicians and Surgeons, at a section meeting on General Practice. New lightweight oxygen apparatus that can be carried by the physician and patient was described. The clinical application of ambulatory oxygen therapy was considered in patients with coronary insufficiency during periods of exertion causing myocardial hypoxia, in those convalescent from coronary thrombosis, and in cases of chronic cardiopulmonary insufficiency. Since the immediate use of oxygen is at times lifesaving in acute coronary thrombosis, it was propounded whether the doctor, or the patient with coronary disease, should carry oxygen with him.

Dr. Virginia Apgar, Research Department of the National Foundation, presented a paper on the Present Status of Knowledge of Human Congenital Anomalies at a section meeting on Pediatrics. Dr. Apgar noted that if the present trend of population increase continues over the next few centuries, the actual number of congenital anomalies will increase in a parallel fashion, although it is doubtful if the mutation rate itself will increase. Observation of several generations will be necessary to determine the true effect of radiation exposure among survivors of the Hiroshima and Nagasaki bomb explosions. In many cases of congenital anomalies, early recognition after birth can lead to proper therapy. Many yield to surgery, if performed soon after birth. Phenylketonuria can be diagnosed in the first week after birth, appropriate diet prescribed, and mental deficiency prevented. By chemical methods, recognition of heterozygotes carrying deleterious genes is becoming more and more possible. Nucleic acid studies and cytologic research may eventually lead to control of chromosomes.

A laboratory technique to aid in the early diagnosis of multiple sclerosis was described by Drs. Robert R. Ivers, Bernard F. McKenzie, Warren F. McGucklin, and Norman P. Goldstein, Mayo Clinic. The method involves a study of lumbar cerebrospinal fluid subjected to electrophoresis on a paper strip. In 72% of 144 cases of typical disease, the content of gamma globulin in a sample was increased. An increase also was noted in 54% of 52 patients who had histories of unremitting multiple sclerosis or initial attacks of the disease. The authors concluded that the content of gamma globulin in the cerebrospinal fluid in the presence of multiple sclerosis, as determined by the paper-strip electrophoretic technique, correlates well with other diagnostic aids but does not correlate with the determination of total proteins in the fluid. An increased gamma globulin fraction is more sensitive and reliable than the other commonly used laboratory tests in the diagnosis of multiple sclerosis, the authors observed. But the procedure (electrophoretic paper-strip) by itself is not diagnostic of multiple sclerosis or any other disease entity. The data in the patient's history and the physical findings are the chief elements in the diagnosis.

Dr. Warren H. Cole, Chicago, told a General Surgery section meeting that any improvements in results after operation for cancer cannot be expected by an extension of the operation. So much tissue already is being removed that removal of more would jeopardize vital structures. Surgeons must adopt new ancillary methods and improve those being utilized to obtain better results. When preparing the patient for operation, Dr. Cole advised, surgeons must not "scrub" with soap and water over any suspicious nodules lest cancer cells be disseminated by the scrubbing process. Tumors must be handled very gently and, if possible, not touched once operability is determined. In cancer of the gastrointestinal tract, attempts should be made to ligate the vascular trunks leading to and from the tumor. In cancer of the colon and small intestine, the lumen of the bowel should be ligated several inches above and below the tumor as soon as operability is determined and the wound should be irrigated with anticancer agents. Nitrogen mustard appears to be effective in cancer of the breast, but not with cancer of the colon and rectum, when used as an adjuvant to surgery.

Hazards of Anesthetization

Drs. Alfred J. Catenacci, John D. Anderson, and Dale Boersma reported on a study of 1,000 obese surgical patients with regard to the hazards of anesthetization. The obese patient was defined arbitrarily as weighing at least 200 lb. and under 5 ft. 6 in. in height.

Because of deficiencies in the mechanics of breathing during inhalation anesthesia, the obese patient usually developed hypoventilation, hypercapnea, and hypoxia with inadequate muscular relaxation. Ventilatory studies showed a greater decrease in pulmonary function in the obese as compared to the nonobese, in the postoperative period. Added precautions in the recovery room were needed to insure adequate ventilation in the obese.

Spinal anesthesia poses two definite hazards in obesity. The first has to do with trauma of lumbar puncture and the second with the controllability of the level of spinal anesthesia.

Dr. Arthur M. Master, New York, reported on the Role of Effort and Occupation in Coronary Occlusion. He said that coronary occlusion is the end-result of an atherosclerotic process and occurs independently of external influences; also that effort does not precipitate acute coronary occlusion, nor does the stress and strain of modern life.

Dr. Master's conclusions were based on 2,600 cases. Information was secured as to the state of activity or rest at the moment of onset of maximum pain, the entire day and the four to six weeks preceding the attack, with particular attention centered on the hour or two just preceding the attack. The subjects ranged from those in the lowest income group to the highest.

The study indicated that occupation was not an important factor; those who are not well just do not enter physically arduous occupations. In 603 episodes where the patient was able to pinpoint the hour in which excruciating pain, collapse, or shock developed, the maximal hours were 2 a. m., 10 p. m., and 11 p. m., periods that are ordinarily not working hours.

Gastroenterology and Proctology

Drs. William F. Lipp and James F. Phillips, Buffalo, N. Y., told the Section meeting on Gastroenterology and Proctology that end-results of treatment of carcinoma of the stomach during a 15-year period ending in 1955 were poor, and there seems little reason for optimism on the basis of experience during the last period from which "five-year follow-up" is possible. It seems unlikely that employment of present methods of diagnosis can result in substantial improvement. There is yet no method for discovering the disease while it is still confined to the stomach. More attention is being directed toward the variability in the behavior of gastric cancer, and it is becoming generally accepted that this can be best explained on the basis of biology of the tumor and immune factors on the part of the host, much as obtains in infectious disease. Clinical evidence for this is now supported by studies of malignant cells circulating in the peripheral blood, known instances of spontaneous regression of tumors, and recent reports suggesting temporary arrest of certain types of cancer through the use of "immune" serums.

Dr. Felix A. Hughes Jr., Associate Professor of Surgery, University of Tennessee School of Medicine, discussed indications for surgical treatment of blastomycosis, histoplasmosis, coccidioidomycosis, aspergillosis, and actinomycosis. He said that amphotericin B appears to be the most effective drug available, while the best surgical results have been in patients with host resistance indicated by a localized process. He also reported that aspergilloma growing in a cystic area of the lung is recognizable clinically and is best treated by resection. Actinomycosis is a medical disease, responding to penicillin, and should be suspected in a patient with a muscle tumor and pulmonary disease.

MEDICAL NEWS

COLORADO

Conference on Education for Foreign Visitors.—Fifty medical educators from 30 countries participated in the fourth annual Conference on Medical Education for Foreign Scholars in the Medical Sciences held June 26-29 in Boulder under the auspices of the University of Colorado School of Medicine. Purpose of the conference was to broaden the perspective of U.S. medical education for the visitors through sessions and discussions with American educational leaders. The registrants are medical educators in their home-lands and are in this country for one or more years of study at various institutions, many of them under Fulbright scholarships issued by the U.S. State Department. The Boulder conference marked the first meeting of the foreign scholars in the Rocky Mountain west. Previous meetings were in Wisconsin and Iowa. Co-sponsors of the conference were the Conference Board of Associated Research Councils; the China Medical Board of New York, Inc.; the Division of International Public Health Service; the Pan-American Sanitary Bureau, World Health Organization; the Rockefeller and Kellogg foundations; and the Association of American Medical Colleges.

DISTRICT OF COLUMBIA

Psychiatric Training Program at Georgetown.—The Georgetown University Medical Center announced a program under which three qualified general practitioners can train in psychiatry for three years with yearly grants of $12,000 maximum. The expanded grant support, appropriated by the National Institute of Mental Health, covers a residency program providing "intensive and varied experience" by utilization of the psychiatric facilities of the Medical Center, D. C. General Hospital, and Mt. Alto Veterans Administration Hospital. To be eligible a physician must have been in practice at least four years following internship, which may include time in the Armed Forces or residency training in some specialty other than psychiatry. Other requirements are graduation from an approved medical school, one year of approved internship, and American citizenship. Applications should be submitted to Dr. Richard A. Steinbach, Department of Psychiatry, Georgetown University Medical Center, Washington, D. C., by Aug. 15.

ILLINOIS

Letter of Dr. Benjamin Rush Presented.—The board chairman of Flint-Eaton division of Baxter Laboratories, Inc., presented an 18th century historical letter, written by Dr. Benjamin Rush, a colonial physician, patriot, and signer of the Declaration of Independence, to Millikin University, Decatur. The university also received a rare engraving of Dr. Rush. The presentation was made in connection with the 1960 commencement at Millikin. The letter from Dr. Rush was written to a fellow Philadelphian, James Broome. It discusses an impending meeting with Dr. Philip Syng Physick, known as the "Father of American Surgery." Dr. Rush, who lived from 1745 to 1813, practiced medicine in Philadelphia beginning in 1769 and was professor of chemistry at the College of Philadelphia from 1769 to 1791 and at the University of Pennsylvania after its merger with the College of Philadelphia in 1791. He was a member of the Continental Congress and served as a surgeon in Washington's Continental Army. He was a member of Pennsylvania's constitutional ratification convention.

Chicago

Dr. Stern Receives Research Award.—Dr. Kurt Stern, associate professor of pathology, Chicago Medical School, was named the recipient of the Dr. Morris L. Parker Award for Meritorious Research. The award of $500 was presented to Dr. Stern for his work on experimental cancer, blood groups, and blood transfusions at the 46th commencement of the school, June 18. Dr. Stern is also director of the Blood Center at Mount Sinai Hospital, and assistant director, Mount Sinai Medical Research Foundation. He received his M.D. at the University of Vienna and was appointed to the school faculty in 1949.

Dustfall in Chicago.—Average total dustfall in Chicago for May was 35.7 tons per square mile, the lowest May average in the records of Armour Research Foundation, conductor of the dustfall survey. The next lowest reading for the month of May was made in 1959: 43.2 tons. A drop in dustfall was noted at all collecting stations except one station on the Southwest side, which exceeded its April reading by 65% (87.3 in May, 53.0 in April). A drop in the average total dustfall in the Loop also was noted in May (47.8 average for May, 97.6 for April). Dustfall readings are recorded at 24 collecting stations in the city.

Hospital News.—Dr. John P. Waitkus, a member of the staff since 1946, was named chairman of the surgery department at St. Bernard's Hospital. Dr. Waitkus is an assistant professor of clinical surgery at the Stritch School of Medicine of Loyola University.——A corner-stone-laying ceremony for the Fantus Out-Patient Clinic Building of Cook County Hospital, 621 S. Winchester Ave., was held May 10. ——Dr. Edmund A. Gorvett, assistant professor of

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

medicine, Northwestern University Medical School was installed as president of the medical staff of Passavant Memorial Hospital at the staff's annual dinner meeting June 2. He succeeded Dr. Emil D. W. Hauser.

MARYLAND

Faculty Promotions at Johns Hopkins.—Five members of the Johns Hopkins medical faculty were promoted to full professor. Drs. Warfield M. Firor and William F. Rienhoff Jr. were appointed professors of surgery. Drs. Samuel P. Asper Jr., John Eager Howard, and Victor A. McKusick were appointed professors of medicine. All are graduates of the Johns Hopkins University School of Medicine, and all received either all or most of their postgraduate training as interns and residents in the Johns Hopkins Hospital. Dr. Firor has been a member of the medical faculty since 1922 and associate professor of surgery since 1929. Dr. Rienhoff, who was resident in surgery from 1923 to 1925, has been a member of the medical faculty since 1921 and associate professor of surgery since 1933. Dr. Asper, a resident in medicine in 1948-1949, has been a member of the medical faculty since 1947 and associate professor of medicine since 1953. He is also associate dean of the medical faculty. Dr. Howard has been a member of the medical faculty since 1932 and associate professor of medicine since 1946. Dr. McKusick, who was resident in medicine in 1951-1952, became a member of the medical faculty in 1947 and has been associate professor of medicine since 1957.

MASSACHUSETTS

Dr. Culver Named Assistant Dean.—The appointment of Dr. Perry J. Culver as assistant dean for admissions at the Harvard Medical School was announced by Dr. George P. Berry, dean of the Faculty of Medicine at Harvard. Dr. Culver succeeds Dr. Kendall Emerson Jr., who resigned, effective June 30, to become medical consultant at the Boston Lying-in Hospital. Dr. Culver will continue to serve as clinical associate in medicine at the Harvard Medical School and as assistant physician at the Massachusetts General Hospital. He has served as a member of the committee on admissions of the Harvard Medical School since 1957.

Announce Endowment of Professorship.—Establishment of three endowed professorial chairs at three of Boston University's professional schools will be part of the activities made possible under the terms of a recent bequest, totalling more than $900,000, made to Boston University by the late Miss Anne A. Ramsey, of Boston. The will of Miss Ramsey makes Boston University a major beneficiary and provides for the direct allocation of $25,000 to apply toward the endowment of a professorship in the University's School of Medicine. It also provides that one-fourth the income of the balance of the estate willed to Boston University be added to endowment of this chair. Professorships will also be established in the university's School of Theology and School of Social Work.

MISSOURI

Dr. Kountz Receives Geriatrics Award.—The Willard O. Thompson Memorial Award "for distinguished contributions to geriatric medicine" was presented to Dr. William B. Kountz, of St. Louis, at the annual dinner of the American Geriatrics Society June 9 in Miami Beach, Fla. A professional society with a membership of more than 7,000 physicians, the society has as its purpose encouraging and promoting the study of geriatrics. The Willard O. Thompson Memorial Award, which includes an honorarium and a medal, is given annually by the society to an "outstanding specialist" in geriatric medicine. At the banquet Dr. Kountz was introduced by Dr. Edward L. Bortz, Philadelphia, president of the society and last year's recipient of the award. Dr. Kountz is assistant professor of clinical medicine, Washington University School of Medicine; consulting physician to Barnes Hospital, Lutheran Hospital, St. Louis Chronic Hospital; member, Board of Control, Division of Gerontology, Washington University School of Medicine, and director of clinical services. He is currently director of scientific research for the Gerontological Research Foundation and vice-president of the International Association of Gerontology.

NEW YORK

Dr. Stannard Becomes Associate Dean.—J. Newell Stannard, Ph.D., professor of radiation biology and associate professor of pharmacology at the University of Rochester School of Medicine and Dentistry, was promoted to associate dean of graduate studies, effective July 1. Dr. Stannard has been acting associte dean of graduate studies for the past year. He has been a member of the faculty of the UR Medical School since 1935, when he came as an assistant in physiology. He became assistant professor in pharmacology in 1947, associate professor and section head of the Atomic Energy Project in 1948, and was promoted to full professor of radiation biology and acting associate dean for graduate studies last year.

New York City

Personal.—Dr. Edgar H. Bates was elected president of the New York University School of Medicine Alumni Association. Dr. Bates, of the class of 1931, took office on July 1.——At the annual meeting of the Food and Nutrition Council of Greater New York May 12, Dr. Seymour Lionel Halpern was elected president. Dr. Halpern, chairman of the Sub-Committee on Nutrition, New York County Medical Society, and a member of the faculty of the New York Medical College, succeeds Dr. Robert S. Goodhart, scientific director of the National Vitamin

Foundation. Dr. Halpern is also president of the Society for Certified Internists of the County of New York.—Dr. Alan F. Guttmacher was named to the post of director of the Margaret Sanger Research Bureau, research and clinical center involved in the study of contraceptive techniques, causes of infertility, marriage education, and marriage counselling. Dr. Guttmacher, clinical professor of obstetrics and gynecology, Columbia University College of Medicine, succeeds the late Dr. Abraham Stone, who died last year.

OHIO

Symposium on Clinical Chemistry.—The Frank E. Bunts Institute, which is affiliated with the Cleveland Clinic Foundation, announced that a symposium in clinical chemistry methods will be held Nov. 9-11, in Cleveland. Topics will include electrophoresis, chromatography, and the measurement of blood pH. Among the speakers will be Dr. Emmett L. Durrum, Stanford, Calif.; S. Raymond Gambino, Milwaukee, Wis., Lena A. Lewis, Ph.D., Cleveland; and Miriam Reiner. Information may be obtained from Adrian Hainline, Ph.D., Cleveland Clinic, 2020 E. 93rd St., Cleveland 6.

OREGON

Record Total for Grants.—More than 3½ million dollars in gifts and grants, the largest total ever recorded, was received during the past year by the University of Oregon Medical School. The 1959-1960 total of $3,661,457 is up half a million dollars from last year's high of $3,108,429. Major portion of the gifts and grants, $2,898,721, was contributed in support of research programs of the Medical School. Included in this total is a $1,297,955 construction grant from the Public Health Service to pay half of the cost of a new Medical Research Laboratories Building. Student aid and scholarship funds accounted for $189,734 of the total, and the instructional program received gifts of $406,181.

TEXAS

Joint Program for Baylor and Paris Colleges.—A joint appointment designed to promote a closer working relationship in the medical sciences between Baylor University College of Medicine and the Collége de France in Paris was announced June 14 by Dr. Stanley W. Olson, Houston, dean of the College of Medicine in the Texas Medical Center. The joint appointment provides that as of July 1, Dr. Roger Guillemin, associate professor of physiology at Baylor also will become associate director of the Institute for Experimental Endocrinology, Collége de France. Under this arrangement, made possible by a grant from the Houston Endowment Inc., Dr. Guillemin will make a division of his time between Houston and Paris. Dr. Guillemin came to Baylor in 1953 as a Markle Foundation fellow in medical science. In 1957, he was awarded a scientific prize by the French Academy of Science, the first such honor to be awarded to an American scientist. Dr. Edward Sakiz, a member of the institute, who has spent six months at the College of Medicine, will be Dr. Guillemin's associate at the Collége de France. The Collége de France, established in 1530, is a research and investigative institution. It reportedly corresponds to the Institute for Advanced Study at Princeton. Its teaching program is directed toward advanced students at the postdoctoral level.

WASHINGTON

Dr. Wagner Goes to New York City.—Dr. Bernard M. Wagner was appointed professor and chairman of the department of pathology at New York Medical College. Dr. Wagner will also serve as director of the department of pathology at the college's Flower and Fifth Avenue Hospitals and at Metropolitan Hospital, a municipal institution affiliated with the college. He is associate professor of pathology and Robert L. King Professor for Cardiovascular Research at the University of Washington School of Medicine, Seattle. From 1956 to 1958, Dr. Wagner served as assistant professor of pathology at the University of Pennsylvania School of Medicine and was also director of pathology at the Children's Hospital of Philadelphia. He received his doctorate of medicine from Hahnemann Medical College.

GENERAL

Contest for Southeastern Hospital Residents.—The Southeastern Surgical Congress announced the prize scientific paper award contest, eligible to residents of approved hospitals in the southeastern states "for the best scientific papers." Papers are due at the Congress Office, 340 Boulevard N. E., Atlanta 12, Ga., before Dec. 1. The prize for the first prize winner is an all-expense paid trip to the meeting at Miami Beach, Fla., March 6-9, 1961, plus a cash award.

Plastic Surgery Meeting in New York City.—The summer meeting of the American Association of Facial Plastic Surgery will be held Friday, July 22, at the Hotel Elysee, New York City. A business meeting and dinner will precede the scientific program. Dr. C. Andrew L. Bassett, assistant professor of orthopedics, Columbia University College of Physicians and Surgeons, New York City, will open the scientific session, presenting "Recent Concepts Concerning Bone Grafts." A colloquy on "Receding Chin" will include the following participants: Dr. Sam H. Sanders, professor of otolaryngology, University of Tennessee College of Medicine, Memphis; Dr. Stanley L. Lane, associate professor of surgery, Albert Einstein College of Medicine, New York City; and Dr. Benito B. Rish, assistant professor of head and neck surgery, Albert Einstein College of

Medicine. For information, write Dr. Samuel M. Bloom, 123 E. 83rd St., New York 28, Secretary.

Section on Medicinal Chemistry Established.—The establishment of a new study section for evaluating research grant applications in medicinal chemistry in the Division of Research Grants was announced by Dr. James A. Shannon, director of the National Institutes of Health, research arm of the Public Health Service. Chairman of the Medicinal Chemistry Study Section is Norman H. Cromwell, Ph.D., department of chemistry, University of Nebraska. The study section is composed of nongovernmental scientists particularly knowledgeable in the fields of chemistry, pharmaceutical chemistry, and pharmacology. All applications for Public Health Service research grants are first reviewed for scientific merit by a study section, a panel of primarily nongovernmental scientists in the general field in which the project falls. The findings are then given further review by one of the national advisory councils. Only on recommendation of a council may the surgeon general award the grant.

Fatal Injuries in Sports.—The Metropolitan Life Insurance Company reported that "although precise data are not available on the number of people injured in organized sports, information from various sources indicates that sprains, strains, and contusions resulting in temporary disability are quite common, and that the annual toll includes many severely injured and not a few deaths." Football accounted for 108 deaths in the United States, during the five-year period 1955-1959, according to data issued by the American Football Coaches Association. Of this total 81 received their injuries in activities directly associated with the game, such as tackling and blocking; tackling was responsible for more than one-fourth of the fatalities directly connected with the game. The 27 deaths indirectly attributable to football were caused by heat stroke, heart failure, and other conditions. Fifty-one of the 81 deaths directly associated with football were among high school players.

In baseball in the professional major leagues, which include more than 400 players, there has not been a fatal injury since 1920. In the past five years, "relatively few fatalities have occurred in amateur baseball, although more than 2 million boys participate in the sport annually as members of scholastic teams, the Little League, American Legion Junior, and similar organizations." The instances of fatal injury resulted from various mishaps: players being hit on the head with a ball while they were batting or running bases; one player was killed when his head hit the base as he was sliding "home," and another, an infielder, was struck on the head with a batted ball during practice. In the years 1955-1959 boxing injuries took the lives of at least 12 amateur fighters and of 6 professionals. Most of these fatalities resulted from mishaps in actual bouts. Five boxing deaths occurred in 1959 alone.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	June 11, 1960		June 13, 1959
	Paralytic Type	Total Cases	Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	1	1	..
Rhode Island	4	4	..
Connecticut	..	..	..
Middle Atlantic States			
New York	..	..	..
New Jersey	..	..	..
Pennsylvania	..	..	..
East North Central States			
Ohio	..	..	2
Indiana	..	..	..
Illinois	..	..	..
Michigan	..	..	3
Wisconsin	..	..	..
West North Central States			
Minnesota	..	..	2
Iowa	..	1	11
Missouri	1	1	1
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	..	..	2
Kansas	..	..	3
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	3
West Virginia	..	..	1
North Carolina	1	1	2
South Carolina	..	..	..
Georgia	..	..	2
Florida	..	..	3
East South Central States			
Kentucky	..	..	..
Tennessee	..	..	2
Alabama	..	..	2
Mississippi	..	..	1
West South Central States			
Arkansas	..	..	3
Louisiana	1	1	3
Oklahoma	..	..	6
Texas	3	4	5
Mountain States			
Montana	2	3	..
Idaho	..	..	..
Wyoming	..	..	..
Colorado	..	..	..
New Mexico	..	..	..
Arizona	..	..	2
Utah	..	..	..
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	..	..	..
California	2	2	12
Alaska	1	1	..
Hawaii	..	..	..
Territories and Possessions			
Puerto Rico	25	25	..
Total	41	44	71

FOREIGN

Otorhinolaryngological Congress in Paris.—The seventh International Congress of Otorhinolaryngology will be held July 23-29, 1961, in Paris, at the

Nouvelle Faculte de Medecine, Rue des Saints-Peres. Topics to be discussed include the following:

Recent advances in pathology and treatment of otosclerosis.
Indications for, and five-year results in, surgical management and combined radiosurgery in the treatment of cancer of the larynx and of the hypopharynx.
The connection between allergy and infections of the nose and bronchi.

Special meetings and social functions are planned for participants of the congress and their wives. Excursions will take place after the congress; the plans for these will be issued before the congress. For information, write the Seventh International Congress of Otorhinolaryngology, Dr. Henry Guillon, General Secretary, 6, Avenue MacMahon, Paris, France.

CORRECTIONS

Approach to the Roentgenographic Diagnosis of Congenital Heart Disease.—In the original contribution entitled "Approach to the Roentgenographic Diagnosis of Congenital Heart Disease," by Owings W. Kincaid, which appeared in The Journal, June 11, pp. 637-647, the last sentence in the third complete paragraph of the left-hand column on page 640 should have read, "In such instances, cyanosis is not usually present."

FAA Ruling on Pilot Physical Examinations.—In the article entitled "FAA Ruling on Pilot Physical Examinations" in the Washington News section of The Journal, May 28, advertising page 27, the Federal Aviation Agency was incorrectly quoted as to results of a survey of private pilots who were awarded medical certificates without meeting the standards set by the agency. The correct FAA statement follows.

"A survey has revealed that of the Class III airmen examined by non-designated physicians, 84 per cent of those who did not meet the medical standards of the Federal Aviation Agency nevertheless were given certificates by the examining physicians."

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, Sept. 7-8. Part II. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

Alaska:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

California: *Written.* Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Connecticut:* Hartford, July 13-14. Sec., Dr. Stanley B. Weld, 160 St. Ronan St., New Haven.

Delaware: *Examination and Endorsement.* Dover, July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

Guam: *Subject to Call.* Sec., Dr. F. L. Conklin, Agana.

Idaho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 358 Sonna Bldg., Boise.

Illinois: *Examination.* Chicago, July 12-14. *Reciprocity.* Chicago, July 15. Supt. of Registration, Mr. Frederic B. Selcke, Capitol Bldg., Springfield.

Massachusetts: *Examination.* Boston, July 12-15. Sec., Dr. David W. Wallwork, Room 37, State House, Boston 33.

Montana: *Examination and Reciprocity.* Helena, Oct. 4. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

Nevada: *Examination and Reciprocity.* Reno, Sept. 7 and Dec. 7. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

New Hampshire: *Examination and Reciprocity.* Concord, Sept. 14-17. Sec., Dr. Edward W. Colby, 61 South Spring St., Concord.

North Carolina: *Examination and Endorsement.* Asheville, July 22. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 13-16. Sec., Dr. C. J. Glaspel, Grafton.

Oregon:* *Examination.* Portland, July 12-13. *Endorsement,* July 14-16. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Puerto Rico: *Examination.* San Juan, Sept. 6-10. Sec., Dr. Herminio Mendez Herrera, Box 9156, Santurce.

South Dakota:* *Examination.* Rapid City, July 19-20. *Reciprocity.* Continuously. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

Washington:* *Examination.* Seattle, July 18-20. *Reciprocity.* Continuously. Administration, Mr. Thomas A. Carter, Capitol Bldg., Olympia.

Wisconsin:* *Examination.* Milwaukee, July 12-14. Sec., Dr. Thomas W. Tormey, 115 So. Pickney St., Madison.

Wyoming: *Written.* Cheyenne, Oct. 3. *Oral for Reciprocity Applicants.* Cheyenne, Oct. 3. Sec., Dr. James W. Sampson, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Colorado: *Examination and Reciprocity.* Denver, Sept. 7-8 and Dec. 7-8. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

New Mexico: *Examination.* Santa Fe, July 17. Sec., Mrs. Marguerite Cantrell, Box 1522, Santa Fe.

Oklahoma: *Examination.* Oklahoma City, Sept. 23-24. Exec. Sec., Mrs. L. Haidek, Braniff Bldg., Oklahoma City.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Madison, Sept. 9. Milwaukee, Dec. 10. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

GOVERNMENT SERVICES

NAVY

Retirement.—Capt. Charles F. Gell, M. C., U. S. N., special assistant for medical and allied sciences at the office of naval research, voluntarily transferred to the Navy's retired list on May 1, 1960, after 39 years of naval service. At retirement ceremonies held at the office of naval research on April 29, Adm. Rawson Bennett presented Dr. Gell with a certificate of exceptional service, taking note of his "outstanding researches in the field of Naval Aviation Medicine, which have contributed significantly to the advance of aeronautical science." The certificate was awarded by the bureau of medicine and surgery.

Portrait of Admiral McIntire.—An oil portrait of the late Vice-Adm. Ross T. McIntire, personal physician to President Franklin D. Roosevelt and chief of the bureau of medicine and surgery of the Navy, was given to the Medical Museum of the Armed Forces Institute of Pathology by the Department of the Navy. The portrait was painted at the White House during World War II by Samuel Bookatz.

PUBLIC HEALTH SERVICE

Water Pollution.—In June, Surgeon General Leroy E. Burney wrote to all state fish and game conservation agencies, asking them to provide continuing reports of fish killed by pollution in rivers, lakes, and coastal waters. Reports will be made directly to the Public Health Service in Washington. On receipt, copies will be made available to the Fish and Wildlife Service of the Department of Interior which is cooperating on the project. The project should be an effective means of obtaining basic information needed to determine the effects of pollution on the nation's water resources, as required by the Federal Water Pollution Control Act. Quarterly and annual reports will be distributed to the cooperating agencies, organizations, and persons who request them.

Nutritional Survey of Colombia.—At the request of the government of the Republic of Colombia, a team of U. S. nutrition experts began on June 6, a 74-day survey of the nutritional status of the Colombian people. The study was arranged by the Interdepartmental Committee on Nutrition for National Defense (ICNND). Dr. Walter G. Unglaub of the Tulane University School of Medicine, New Orleans, heads the team of clinicians, biochemists, nutritionists, dentists, food technologists, and others who, along with counterpart Colombian personnel, will examine large sections of the civilian and military population in order to obtain information on current nutritional conditions. The team will formulate practical recommendations for nutritional improvement consistent with Colombia's resources and will provide assistance for the development of standard ration requirements and local nutrition services.

Laboratory equipment and supplies to be used in the survey have been shipped to Bogota. At the conclusion of the study, the equipment will be given to the Colombian government under provisions of the Mutual Assistance Program for use in operating permanent nutrition services. The ICNND, operating administratively through the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md., is headed by Dr. Frank B. Berry, assistant secretary of defense, health and medical, with Dr. Arnold E. Schaefer as executive director. Cooperating U. S. agencies include the Departments of State; Health, Education, and Welfare; Defense; Agriculture; and the International Cooperation Administration.

Members of the Colombia Survey Team include: Dr. Robert E. Parks, University of Wisconsin, Madison, Wis., clinician; Dr. Paulus Zee, a pediatrician from The Netherlands who is currently attached to the Tulane University School of Medicine, clinician; Dr. John J. Kevany, Instituto Nacional de Nutricion, Quito, Ecuador, clinician; Dr. Joseph J. Vitale, Department of Nutrition, School of Public Health, Harvard University, Boston, laboratory director; Dr. O. Neal Miller, Tulane University School of Medicine, biochemist; Dr. Zeki M. Tolgay from Turkey, currently serving as research associate at the National Institutes of Health, biochemist; Dr. Hernan Velez and Dr. Alfonso Villamil, both of Colombia and serving as fellows at the Tulane University School of Medicine, biochemists; Dr. Alfredo Lopez, from Spain, currently serving as fellow in nutrition and metabolism at Tulane University, biochemist; Major Leo V. Crowley of the Walter Reed Army Institute of Research, Washington, nutrition officer; Dr. Elmer W. Hartsook, Pennsylvania State University, University Park, Pa., assistant nutrition officer; Dr. Willard B. Robinson, New York State Agricultural Experiment Station, Cornell University, Geneva, N. Y., food technologist; Dr. Charles J. Donnelly, National Institute of Dental Research, National Institutes of Health, dentist; and Mr. Durward R. Thayer, Communicable Disease Center, Atlanta, Ga., medical photographer.

Personal.—Dr. Robert J. Anderson was appointed deputy chief of the bureau of state services. He will report for duty on July 1 and will succeed Dr. Theodore J. Bauer, whose appointment as chief of the bureau, effective the same date, was announced earlier.

DEATHS

Atkinson, Charles Edwin, Banning, Calif.; University of Southern California College of Medicine, Los Angeles, 1907; member of the American College of Chest Physicians and the American Trudeau Society; past-president of the Riverside County Medical Society; for many years medical director of the Southern Sierras Sanatorium; served as medical consultant at the Riverside County Hospital; author of "Lessons on Tuberculosis and Consumption"; died at St. Bernardine's Hospital in San Bernardino May 5, aged 75, of subdural hematoma.

Bernstein, William S., Brooklyn; Long Island College Hospital, Brooklyn, 1925; died April 11, aged 59, of myocardial infarction.

Blitzer, Nathaniel, Brooklyn; Baltimore Medical College, 1902; died in the Kings County Hospital March 28, aged 80, of myocardial infarction.

Blutman, Harry Austin, New York City; University of St. Andrews Conjoint Medical School, St. Andrews and Dundee, Scotland, 1934; died Feb. 15, aged 56, of myocardial infarction.

Bokor, Emery Ⓜ Newark, N. J.; Magyar Kiralyi Pazmany Petrus Tudomanyegyetem Orvosi Fakultasa, Budapest, Hungary, 1911; on the staff of the Beth Israel Hospital; died May 12, aged 71, of cerebral hemorrhage.

Brown, Harry Weller, Des Moines, Iowa; State University of Iowa College of Medicine, Iowa City, 1906; associated with the adjudication department of the Veterans Administration; formerly practiced in Waterloo, where for many years he was district physician for the Illinois Central Railroad; died in the Iowa Methodist Hospital May 9, aged 79, of lymphosarcoma.

Carp, Solomon Philip, New York City; University and Bellevue Hospital Medical College, New York City, 1927; member of the American Rheumatism Association; died March 22, aged 57, of carcinoma of the descending colon.

Carter, John Gailard Jr. Ⓜ Scott, Ga.; Atlanta Medical College, 1915; died April 28, aged 77, of intestinal obstruction.

Cooper, Theodore Ⓜ Baltimore; Yale University School of Medicine, New Haven, Conn., 1931; member of the American Trudeau Society; died in Sinai Hospital April 12, aged 55, of uremia.

Cowen, Edward David, Roaring Spring, Pa.; Bennett Medical College, Chicago, 1890; died in the Nason Hospital April 14, aged 96, of arteriosclerosis with renal failure.

Culpepper, William Stephen, Colonel, U. S. Army, retired, Alexandria, Va.; Birmingham (Ala.) Medical College, 1911; specialist certified by the American Board of Otolaryngology; fellow of the American College of Surgeons; veteran of World Wars I and II; entered the U. S. Army in 1918 and retired Oct. 31, 1947; died in the U. S. Army Hospital, Fort Benning, Ga., April 9, aged 73, of pulmonary edema due to arteriosclerotic heart disease.

Dangler, Henry William, Brooklyn; Long Island College Hospital, Brooklyn, 1907; fellow of the American College of Surgeons; on the staff of the Bushwick Hospital; died March 27, aged 77, of myocardial insufficiency.

Donovan, Jeremiah John, Randolph, Mass.; Harvard Medical School, Boston, 1914; for many years associated with the U. S. Public Health Service; veteran of World War I; died in the Veterans Administration Hospital, Boston, May 2, aged 80, of occlusion of the right common carotid.

Estridge, Floyd Gilbert, Lancaster, Ky.; University of Tennessee College of Medicine, Memphis, 1932; interned at the Meriden (Conn.) Hospital; on the staff of the Garrard County Memorial Hospital; died in the Pattie A. Clay Infirmary, Richmond, April 30, aged 52, of coronary occlusion.

Farley, Roger Truman, Chicago; College of Medicine and Surgery (Physio-Medical), Chicago, 1901; member of the American Academy of General Practice; affiliated with Jackson Park Hospital; died April 23, aged 82, of acute coronary occlusion.

Fromm, Hyman, Brooklyn; New York Homeopathic Medical College and Flower Hospital, New York City, 1921; died Feb. 11, aged 75, of acute myocardial infarction.

Gerber, Milo Phil, West Palm Beach, Fla.; University of Minnesota Medical School, Minneapolis, 1921; formerly practiced in Brainerd, Minn.; veteran of World War I; died April 29, aged 68, of hemorrhage from gastric ulcer.

Granger, Carl Victor C. Sr., Huntington Station, N. Y.; University and Bellevue Hospital Medical College, New York City, 1927; associated with the Huntington (N. Y.) Hospital; died May 12, aged 58, of pulmonary edema.

Halloran, William Herman Ⓜ Audubon, Iowa; the Hahnemann Medical College and Hospital, Chi-

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Ⓜ Indicates Member of the American Medical Association.

cago, 1909; formerly county coroner; city health officer; died May 3, aged 77, of cancer of the tongue and mouth.

Hamilton, Frank Errett, Beaufort, S. C.; University of Pennsylvania School of Medicine, Philadelphia, 1930; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; veteran of World War II; resigned from the regular Army July 10, 1950; at one time on the faculty of the Ohio State University College of Medicine in Columbus; died in the Medical College of South Carolina Hospital, Charleston, S. C., April 28, aged 55, of acute hepatic failure.

Herrman, Charles, New York City; Columbia University College of Physicians and Surgeons, New York City, 1895; at one time on the faculty of his alma mater; specialist certified by the American Board of Pediatrics; veteran of World War I; formerly on the staffs of Riverside and Lebanon hospitals; died April 4, aged 86, of carcinoma of the sigmoid colon with metastases.

Holman, Russell Lowell Ⓜ New Orleans; born in Conway, Ark., Jan. 29, 1907; Vanderbilt University School of Medicine, Nashville, Tenn., 1931; specialist certified by the American Board of Pathology; professor of pathology at the Louisiana State University School of Medicine, where he was head of the department; served on the faculty of the University of Rochester School of Medicine in Rochester, N. Y., Columbia University College of Physicians and Surgeons in New York City, and the University of North Carolina School of Medicine, Chapel Hill; chairman of the Section on Pathology and Physiology of the American Medical Association; served as secretary of the American Association of Pathologists and Bacteriologists; immediate past-president of the Greater New Orleans Association for Retarded Children; past-president of the American Society for the Study of Arteriosclerosis and the American Society for Experimental Pathology; member of the College of American Pathologists, American Society for Experimental Pathology, and the American Society of Clinical Pathologists; a member of the National Research Council, and a member of the pathology study section of the National Institute of Health; senior visiting pathologist at the Charity Hospital; from 1937 to 1946 visiting pathologist at the Watts Hospital in Durham, N. C.; died May 5, aged 53, of cancer of the lung.

Holt, Richmond Reid, Parrott, Ga.; Atlanta Medical College, 1914; veteran of World War I; on the staff of the Terrell County Hospital, Dawson; died April 28, aged 68, of coronary occlusion.

Hoover, John Roderic Chase, Haddam, Kan.; University of Nebraska College of Medicine, Omaha, 1925; veteran of World War I; died in the Washington County Hospital, Washington, Feb. 29, aged 63, of bronchopneumonia.

Pollack, Fredolph A., Norfolk, Neb.; John A. Creighton Medical College, Omaha, 1917; fellow of the American College of Surgeons; affiliated with Lutheran Community and Our Lady of Lourdes hospitals; died in Nebraska Methodist Hospital, Omaha, May 12, aged 71, of injuries received in an automobile accident.

Pollock, Isador Ira Ⓜ New York City; Jefferson Medical College of Philadelphia, 1929; affiliated with Harlem Hospital and the Bronx Hospital, where he died May 10, aged 58, of left subphrenic abscess due to splenectomy.

Spencer, Eugene Spitzer Ⓜ Kew Gardens, N. Y.; Medizinische Fakultät der Universität, Vienna, Austria, 1924; served a residency at the Nathan Littauer Hospital in Gloversville; member of the American Society of Anesthesiologists; fellow of the International College of Surgeons; died in the James Ewing Hospital, New York City, April 26, aged 60, of chronic lymphocytic leukemia.

Spicer, Richard Williams, Winston-Salem, N. C.; University of Pennsylvania School of Medicine, Philadelphia, 1911; North Carolina Medical College, Charlotte, 1910; veteran of World War I; died in the Veterans Administration Hospital, Salisbury, May 3, aged 73, of cardiac failure.

Stansbury, Thomas Conley Jr., Sarasota, Fla.; University of Louisville (Ky.) School of Medicine, 1946; interned at the University Hospitals in Iowa City, Iowa; held a fellowship in radiology at the University of Minnesota Hospital in Minneapolis, where he served a residency at the Minneapolis General Hospital; served a residency at the Veterans Administration Hospital in Fort Howard, Md.; specialist certified by the American Board of Radiology; member of the American College of Radiology; from 1947 to 1949 captain in the medical corps, Army of the United States; associated with the Memorial Hospital; died May 3, aged 37, of a subdural hemorrhage incurred in an automobile accident.

Wiener, Kurt Ⓜ Milwaukee; Schlesische-Friedrich-Wilhelms Universität Medizinische Fakultät, Breslau, Prussia, Germany, 1915; specialist certified by the American Board of Dermatology; member of the American Academy of Dermatology and Syphilology; associated with the Evangelical Deaconess, St. Michael, and Mount Sinai hospitals; author of "Skin Manifestations of Internal Disorders" and "Systemic Associations and Treatment of Skin Diseases"; died May 6, aged 68, of chronic leukemia.

Wilkinson, Elisha Thomas, Albuquerque, N. M.; Louisville (Ky.) Medical College, 1893; died in the Presbyterian Infirmary Jan. 8, aged 88, of hypostatic pneumonia.

FOREIGN LETTERS

BRAZIL

What Is Surgical Mortality?—In his 1959 report on the activities of the Hospital São Miguel in Rio de Janeiro, Dr. Fernando Paulino stressed the importance of defining "surgical mortality." In this hospital, 972 patients were operated on during the year, and of these 15 died, a surgical mortality of 1.54%. In this hospital a death is considered surgical when the patient dies in the first 15 days after the operation even from causes not directly related to the operation or when the patient dies up to 6 months after the operation, either in the hospital or at home, if death was due to complications related to the operation. The time elapsed between the operation and death in this series varied between 24 hours and 3 months (average 10 days).

The author is opposed to the inexact use of such expressions as operative, postoperative, late surgical, and delayed deaths. He believes that the term "late surgical death" refers, as a rule, to the outcome of operations performed for cancer or other grave or relapsing disease in which the patient, even though surviving the operation, may die from a relapse of the disease. In such a case, the phrase "late surgical death" is not self- explanatory and the death should be recorded as due to the underlying disease.

South American Blastomycosis.—The definitive diagnosis of South American blastomycosis is made by the recognition of Blastomyces brasiliensis in exudates or in lesions. The only difficulty arises, in some cases, from the deep situation of the diseased organ. The generally accepted but erroneous idea among physicians that the diagnosis is difficult delays the recognition of the disease and prevents early and efficient treatment. Drs. J. Miranda and J. Machado Jr. *(Hospital, Rio de Janeiro* 56:579, 1959) analyzed the mycological diagnosis of 261 positive cases. Most of these patients were white men who worked in rural areas. In this series 37 patients (14.2%) had superficial lesions only; 30 (11.5%) had systemic lesions only; and 194 (74.3%) had both systemic and superficial lesions. The authors show that fresh direct microscopic examination and histopathological examination will confirm the diagnosis. The first technique alone permitted the diagnosis in 98 (37.5%); the second technique alone in 46 (17.6%); and the use of both examinations in 117 patients (44.9%).

The direct microscopic examination of sputum was performed on 164 patients, alone on 20, and in combination with other examinations in 144. It furnished the only positive basis for the diagnosis in 22 patients and was positive in 102 (62.2%) of those on whom it was used. The direct examination of pus from lymph nodes was performed on 22 patients and was the exclusive basis for the diagnosis of the disease in 10. Its positivity rate was 100%. The direct microscopic examination of a fragment of lesion, collected by scraping or biopsy, was used alone for the diagnosis of 20 patients and combined with other examinations for 112 more patients. It was negative in only two patients, thus giving a positivity rate of 98.2%. The histopathological examination was performed on 163 patients, having been the only method of examination for the diagnosis of the disease in 41 patients and in 5 autopsies. It was used for 117 patients in association with the microscopic examination; in the total 163 cases it was negative in only 2, thus showing a positivity rate of 98.8%. It was found that more than 50% of the patients had been sick for periods longer than nine months (up to three years) before the diagnosis was established, and the case histories suggest that in a large number of patients the physicians did not even suspect the disease.

FINLAND

Trigeminal Neuralgia.—G. af Björkesten (*Acta chir. scandinav.* 117:446-450, 1959) reported a series of 46 patients who had trigeminal neuralgia and on whom a decompression of the gasserian ganglion and the trigeminal root was performed. There were no operative deaths. In all patients the neuralgia disappeared completely. Seven developed a facial paralysis postoperatively, but this later disappeared. There were no postoperative corneal complications. The series showed slightly more than 20% recurrence after a follow-up period of one to five years and a somewhat smaller incidence of continuous atypical facial pain. Some of the recurrences and all instances of continuous facial pain were, however, slight and required no special treatment. The incidence of postoperative sensory disturbances in this series was somewhat higher than in previous reports. The author concluded that, in spite of the comparatively high incidence of recurrence, the decompression operation was justified. Because many of the recurrences and the other postoperative disturbances were very slight, the practical results were better than the bare statistics would indicate.

The items in these letters are contributed by regular correspondents in the various foreign countries.

INDIA

Use of Testosterone in Underdeveloped Children.—Bhatt and Merchant (*Indian J. Child Hlth.* 9:186 [April] 1960) treated 55 children (18 girls and 37 boys) whose growth was retarded with testosterone; 21 others served as controls. The patients were brought to the hospital for failure to put on weight and height normally. Any systemic cause for retarded growth was excluded. Roentgenograms of carpal bones were used to estimate the bone age, and patients whose bone age was markedly less than their chronological age were selected for study. They were given 5 mg. of methyl testosterone daily by mouth for three months. The parents were instructed to encourage sublingual administration insofar as possible. The children were followed up for a year. One group of controls received a general tonic, and another group, after taking the tonic for six months, was given testosterone. The ages of the children ranged from 6 months to 12 years.

The late effects of male hormone administration to girls were not observed because the period of observation was comparatively short. Although the hormone could be absorbed from the gastrointestinal tract, it was found to be more active when given sublingually. The response was better in the group that sucked the tablets than in those who swallowed them. Sublingual administration was not possible in the age group of under 1 to 4 years of age, and the results were comparatively less pronounced than those in the older children. Larger doses were required to produce the same effect when the tablets were swallowed.

Most of the parents were satisfied with the improvement in the appetite and activity of the children after treatment. Secondary effects on the external genitals were less common in the younger children. They were sometimes marked in the older children, requiring a reduction in the dose or cessation of treatment, but these effects were transitory. A distinct gain in height and weight was noticed in the children receiving the hormone as compared to the control group. This effect was sustained for at least one year as shown by follow-up examination. Whether these children would later have an early epiphyseal closure as a result of hormonal treatment could not be ascertained in this study, but the authors advised that testosterone should be avoided if the bone age and chronological age coincided or the former was in advance of the latter. The small doses used here probably would not prevent attainment of the expected height. The response attained was best in the group 5-to-8-year age group, fair in the 9-to-12-year age group, and in the 0-to-4-year age group the weight gain was significant compared to that of the controls. Improved development was seen in both girls and boys, and the results were encouraging.

Vegetable Protein Diets for Kwashiorkor.—G. P. Rao (*Indian J. Child Hlth.* 9:207 [April] 1960) gave a mixture of cheap vegetable proteins to 24 children with kwashiorkor. The mixture consisted of defatted ground-nut flour and Bengal gram flour. Fourteen children were given skimmed milk powder and served as controls. Eleven of the experimental group were given injections of vitamin B_{12} on alternate days, as vegetable proteins are believed to be inferior to animal proteins because of the absence of vitamin B_{12}. The caloric intake in all groups was kept about the same. The protein content of the skimmed milk diet was 57 and that of the vegetable diet was 60 Gm. per day. The time taken for disappearance of edema with all types of treatment was about the same. A close relationship was observed between the time taken for disappearance of edema clinically and that for reaching minimum normal body weight. The total weight gain of children on the 30th day of treatment was also nearly the same. Manifestations such as skin lesions, hair changes, anemia, hepatomegaly, and mental changes showed similar improvement in all. The number of cases studied and the period of observation was too small to justify definite conclusions, but the results were encouraging and, if confirmed, would help to solve the problem of malnutrition which is so prevalent in India.

JAPAN

Juvenile Hypertension.—In 1957 a blood pressure survey of 2,400 school children was made. Those below the fifth grade were all found to have pressures within the normal limits. Of 1,100 pupils who were 11 years of age or older, however, 15 had a high blood pressure. In these 15, dizziness and headache were common symptoms. Some participated greatly in school athletic programs. They were all found to be hearty rice eaters with an unusually high intake of salt. The parents of these children were also found to have hypertension. The children were urged to adapt a diet conducive to hypotension, but after a follow-up of several years no improvement was noted.

Shortage of Nurses.—Because of an inadequate supply of nurses, the city hospital of Takada asked its married nurses to postpone motherhood. One nurse objected and took her case to the solicitor general's office, contending that it would tend to destroy her family. Superintendent Dr. Sotogoshi Sakata replied that because of the dearth of nurses, absenteeism among the married nurses for any cause would place an undue hardship on those remaining on duty. Nevertheless the court ordered him to rescind the rule as it was clearly an invasion of personal liberty and the privacy of the family.

SWEDEN

Complications in Mitral Commissurotomy.—The occurrence of fresh thrombi in the left atrium in patients with mitral stenosis constitutes a serious complication from the viewpoint of cardiac surgery. During the operation such thrombi may become detached and give rise to embolism which may threaten the life of the patient. In preoperative care therefore, as in conservative treatment, one must try to preclude the formation of intracardiac thrombosis or to accelerate the organization of already existing thrombi and prevent further agglutination of these.

Lars-Erik Carlgren and co-workers (*Acta chir. scandinav.* [supp.] 245:184-192, 1959) reported a series of 100 consecutive operations for mitral stenosis. Sixteen patients had a history of systemic embolism, and thornbi in the left atrium were found in eight more at operation. The total incidence of verified preoperative thromboembolism in this series was 24%. In 29 patients calcified cusps were found at operation. The total morbidity in regard to thrombotic and embolic complications or both in connection with operation was 6% (4% primary and 2% secondary). The total mortality was 2%. All patients with a history of clinically established or suspected embolism were given bishydroxycoumarin, either continuously or for several weeks after the embolic episode. Several patients who had not had emboli were also given this drug prophylactically, sometimes for months, but as a rule only for the few weeks immediately preceding operation. In all, 11 of the 50 patients with sinus rhythm and 35 of the 50 with fibrillation were treated with anticoagulants. The favorable effect of bishydroxycoumarin in patients with recurring embolism supported the inclusion of such prophylaxis in the preoperative treatment of mitral stenosis. This prophylaxis should not be restricted to patients with a history of embolism, but other patients with atrial fibrillation and those with marked enlargement of the heart should also be treated with anticoagulants.

The indications must be weighed against the risks and the practical difficulties connected with such treatment. In blind operations in the left heart, a careful palpation of the atrium is necessary. In all patients in this series, palpation was done with the bare finger which permitted a more precise and less traumatic palpation of possible thrombi and a better assessment of their degree of organization. It is also important to make a careful palpation of valvular calcification before commissurotomy is undertaken. In patients in whom there is risk of embolism, the carotid arteries should be temporarily clamped bilaterally as recommended by Bailey. This would preclude the possibility of major embolism in the carotids, but as was apparent from these observations, it was no guarantee against small emboli in the fine cerebral arteries.

Sliding Esophageal Hiatal Hernia.—Werner and Wiklund (*Acta chir. scandinav.* [supp.] 245:173-183, 1959) reported a series of 50 patients operated on for sliding hernia in the esophageal hiatus. The oldest patient was aged 78 years and the youngest aged 10 (average 54). The hernias were commonest in the age group 50 to 70 years. A varying technique for the repair of hiatal hernias was applied during the 17 years covered by the study. In the earlier years most operations were performed transthoracically, but in recent years most were transabdominal; 18 patients were operated on through the thorax and 32 through the abdomen. Among the 45 survivors there were 4 who had recurrences. There were no recurrences in the group operated on transabdominally. The authors concluded that the abdominal approach was the more suitable of the two used because (1) if one operates through the abdomen, one can also explore the abdomen and determine whether the symptoms were caused by the hernia or by an abdominal affection, (2) any operation for cholelithiasis, peptic ulcer, or other abdominal disease that may be indicated can be undertaken at the same time, and (3) every thoracotomy is associated with the risk of impairment of pulmonary function.

UNITED KINGDOM

Plethora of Polishing.—Some domestic jobs done in hospitals are a waste of time according to a report of the Ministry of Health. These include polishing of metal door handles, light switches, and cup hooks. The report also suggested that cutlery is often polished to excess, particularly the cutlery used in senior staff dining rooms. In extreme cases polish was applied three times a day. Polishing of metal work such as door handles could be saved by painting over it, but some staffs, in misplaced enthusiasm for brightly polished metal work, scrape off the paint and repolish the metal. The cost of domestic work in hospitals in England and Wales is reported as over $50 million a year.

Droplet Infections.—The leading editorial of the *British Medical Journal* (April 30, 1960) stated that when a healthy person remains silent no organisms come from his mouth or nose but that when he speaks, coughs, or sneezes large numbers of the commensal organisms usually present in the nasopharynx, such as Streptococcus salivarious, Streptococcus viridans, and Neisseria catarrhalis, are expelled into the air. The assumption was therefore made many years ago that, if pathogenic organisms such as Streptococcus pyogenes and Staphylococcus aureus are also present in the nasopharynx, they will be expelled in sufficient numbers to justify the wearing of masks as part of the ritual of an operating or delivery room. Nevertheless, it has not been shown that these two pathogens are expelled in large numbers. In the case of Str. pyogenes it was first found by Bloomfield and Felty, in 1924, and since then by others, that both carriers and patients with tonsillitis or scarlet fever expelled so few organisms when talking, coughing, or sneezing that culture plates held in front of the mouth were usually found to be free of this organism.

Even when a carrier puts himself into the same position as a surgeon while performing an operation and talks in a fairly loud voice for five minutes directly downward onto a culture plate 12 in. (30 cm.) away, he may fail to project this organism onto it. In one series of experiments only 3 of 12 carriers were able to do so, and even when this organism did appear on the culture plates not more than one or two colonies were obtained. The probable reasons for the infrequency with which this Streptococcus leaves the mouth would seem to be that it can be expelled only in droplets, that these droplets consist of saliva derived almost exclusively from the front of the mouth, and that, for some as yet unknown reason, the saliva in this part of the mouth contains few Str. pyogenes, even when the subject is in the throes of an active infection such as tonsillitis or scarlet fever.

Staph. aureus is found so infrequently in the mouth that its expulsion in droplets of saliva is improbable. It parasitizes a small area of skin in the front of the nose. The air passing over this area when the person remains silent does not pick it up as it does not appear on culture plates held directly beneath the nostrils. If it emerges it is more likely to do so in droplets, but it is improbable that droplets are expelled in any number. Examination of flashlight photographs during activities such as talking and coughing, which bring about the expulsion of large numbers of droplets from the mouth, show clearly that comparable numbers of droplets are not expelled from the nose. Indeed, even when a person sneezes few emerge from the nasal orifices. It is not surprising, therefore, that when culture plates are held beneath the nose of a person who is talking, coughing, or sneezing they collect few organisms of any kind, and even if the subject is a nasal carrier of Staph. aureus the absence of this organism is generally conspicuous. Confirmation of this has recently come from Shooter and co-workers.

It is concluded that so few droplets carry pathogenic organisms that almost anything placed in front of the mouth will suffice to catch them, and, if it is possible to impose a complete ban on conversation, nothing at all need be worn. There is much to be said for the second alternative, because a mask that has been worn for some time can become dangerous as it comes into close contact with the nose and upper lip, both areas that are heavily contaminated by Staph. aureus when the wearer is a carrier. The mask can, accordingly, become a carrier in turn. Examination by Shooter and his colleagues of 53 masks after use for some time by nasal carriers of this organism in the operating room showed that 33 were contaminated on the inside and 21 on the outside. If such a mask is handled or put into the pocket, both the fingers and the clothing of the carrier will become more heavily contaminated by his own organisms than they would have been if he had not been provided with a mask.

Family Doctor.—If the family doctor is to survive he must learn to manage his patients' psychological as well as his physical problems. This view was put to the Royal Society of Health congress by Dr. C. A. H. Watts, a family doctor. He added that there is still room for a jack-of-all-trades, but he must be a master of one, personal medicine. Fifty years ago the doctor had practically no weapons with which to fight disease. Now he is wonderfully equipped, yet his status has fallen because he has ignored the extremely important matter of personal relationships.

Atomic Sterilization.—Within the next 18 months three irradiation plants in Britain will sterilize medical equipment; all will be operated by private industry. This $2,500,000 project was initiated four years ago as an offshoot of the Atomic Energy Research Establishment. The most advantageous use of radioactive isotopes so far has been the sterilization by radiation of such medical equipment as plastic syringes, gloves, catheters, swabs, blankets, and scalpels. A large pilot plant will soon be put into operation. Anything that can be put in foot-cubed packages can be sterilized at this plant. The packages are carried on a moving belt past an extremely radioactive source of cobalt-60. The speed can be regulated so that the packages can spend from 6 minutes to 40 hours being irradiated.

At one time it was thought that food sterilization and preservation might form an important part of the work of the plant, but the difficulties of retaining the customary flavor, odor, and color have been great. The most promising irradiation of food at present concerns the inhibition of sprouting in potatoes and the increased length of life of refrigerated meat. Potatoes can be prevented from sprouting at a cost of a penny a hundredweight. Such bacteria as Salmonella and Clostridium botulinum can be killed satisfactorily by this method, and the growth of molds on fruits and vegetables can be inhibited. Otherwise the applications to foods are unpromising. Another important advantage of this procedure is prevention of infestation in grain and other food. The dose required to kill grain weevils does not affect the grain itself.

CORRESPONDENCE

COLOR DESCRIPTION

To the Editor:—In science, art, and industry, the descriptive terms such as very pale, very light, brilliant, light, moderate, and medium suggested in the letter by Dr. Appel in The Journal, April 23, page 1971, may be adequate and acceptable, but the concern of a teacher or of a writer is to describe color to students, as well as to the conference of the experts, in a readily understandable way. Scientifically, it is appropriate to use the terms very pale, very light, brilliant, very brilliant, moderately brilliant, and dozens of varieties of the kind because eventually the scientist will refer to his Munsell Book of Colors or the ISSCC-NBS Method of Designating Colors.

If one is to stick unequivocally to science, one should not use the terms carbon-dioxide snow, orange or olive color, butterfly rash, rusty sputum, ivory white, or map-of-Maine and map-of-California hyperpigmentation because the student may come from countries where there are no snow, oranges, olives, butterflies, or rust and may never have heard of Maine, California, or ivory. Until physicians agree on a standard chart of about 50 colors for use in class and for reference in textbooks and publications, they should be less uncertain and use the cardinals and the salmons in moderation, as adjunctives, rather than expect the student to fix in his brain, in a few hours of clinical dermatology, the color of a dermatosis from words such as Dr. Appel suggests.

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DIELDRIN INTOXICATION

To the Editor:—In The Journal, April 30, page 2077, is a report from the Committee on Toxicology which is in many ways misleading in its implications and may have results which were not intended by the committee. The report in question, "Occupational Dieldrin Poisoning," purports to review chronic occupational intoxication. It is not possible to determine from the report what is meant by the term "chronic." Does this refer to long-continued illness resulting from a single exposure, only to those from multiple exposures, or only to long-continued (chronic) exposure without reference to the duration of illness? To me, chronic occupational illness means illness of occupational origin persisting for a long time. There is some question as to whether dieldrin is capable of causing a chronic clinical illness, although electroencephalographic changes may persist for some time after the acute syndrome. The one new case reported in the review is an acute case by any definition.

I have been collecting reports of intoxications from insecticides for several years. In the past few years there has been an almost complete absence of reports of dieldrin poisoning in the United States despite its widespread agricultural use. Dieldrin, contrary to the statement in the review, is approved and widely used as a residual spray for indoor application. It is not approved for use as a space spray, a quite different type of use.

I believe that this review will lead practicing physicians into the mistaken belief that "chronic occupational dieldrin poisoning" is a significant problem. Careful reading of the article reveals not a single reference to dieldrin intoxication in the United States. Many of the reports cited leave much to be desired inasmuch as they do not establish the existence of a chronic syndrome, for most of the reports originated from relatively remote areas where adequate opportunity for a careful appraisal of all possible complicating factors was not possible.

I have found that dieldrin intoxication has occurred in the United States only when safety precautions were flagrantly ignored or when ingestion occurred by accident or design. There is no record in this country of any chronic effects or of any residual damage. Cases of such intoxication are rare, and it would be regrettable if the implication were to be drawn that the committee had written this review because a problem existed in the United States.

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STATUS LYMPHATICUS

To the Editor:—In The Journal, April 16, page 68, "From Other Pages" is a portion of a paper by Dr. W. B. Bean entitled "Mythical Maladies." Referring to the belief that an enlargement of the thymus gland might in some way be responsible for sudden death in infants, Dr. Bean said, "Legend has it that status lymphaticus was recognized 300 years ago. Actually it had no currency before the early years of the present century. Its origin probably lies in a paper published by Paltauf in 1889." Finally, he stated that "In the 1930's it seemed increasingly probable that physicians were fretting about a nonexistent disease."

There is material available which provides unquestionable evidence that the subject of thymic enlargement and its implications were thoroughly discussed much earlier than 1889. I have recently been perusing some old volumes of *The Medical Times and Gazette* (London). In the issue of Aug. 15, 1857, page 164, there appeared a paper by William Pretty entitled "On the Large Growth of the Thymus Gland as a Cause, Real or Supposed, of the Sudden Deaths of Infants." In his discussion of this subject, Mr. Pretty reported the histories of six infants whose deaths occurred suddenly and unexpectedly and in whom grossly enlarged thymus glands were disclosed at autopsy. He, however, was personally far from convinced that these thymic enlargements accounted for the deaths, particularly since in most of the patients there were other lesions that he considered were more likely to have been responsible.

Four weeks later, in the issue of Sept. 12, 1857, page 280, appeared a letter from W. Newman, of Fulbeck, Grantham, reporting a case of sudden death of a 9-month-old infant in which the only significant autopsy findings were a "serious cerebral lesion, unmarked by external signs," and a thymus that was "very large, pale, and flabby . . . [which] occupied the whole of the anterior mediastinum superiorly." The cerebral lesion apparently was in the nature of a meningitis, and the correspondent expressed the opinion that "the arachnitis would probably give rise to fatal irritation of the brain without the necessity of supposing the thymus gland in any way concerned in such a result." Thus, long before the 1930's doubts began to arise as to how much significance could be attached to the thymus as a factor in sudden death.

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A DEATH FROM TETANUS

To the Editor:—On Nov. 1, 1959, Connecticut had another tetanus death. It represented one more unnecessary loss of life from a completely preventable disease. The victim was said to have spread petroleum jelly over the wound, effectively sealing out the air. He had incurred "deep lacerations" while climbing a barbed wire fence. Bleeding presumably followed, and the petroleum jelly would seem to have been used to check this bleeding. There are numerous "soothing, antiseptic" creams on the market for home use on wounds; also, plastic sprays to stop bleeding are being offered to the public. To my knowledge, none of the products in either category claim to kill tetanus spores. It seems that the trusting use of these by mothers and other administrators of first aid would set up ideal anerobic conditions for the development of tetanus in unvaccinated persons. With the fairly widespread immunization of children nowadays this may not be much of a problem, but an episode with such a cream or spray may cause tetanus in any inadequately protected person.

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CARBOLATED PETROLEUM JELLY

To the Editor:—Some six months ago a 74-year-old woman wore a tight shoe in which there was a bow and a knot that tied behind her heel which caused a blister. After this she used carbolated petroleum jelly, which I did not know was still on the market, and it sloughed the skin for an area 2 in. in diameter over her tendo achillis. Her leg shows no tendency to numbness. She has been referred for plastic repair. Anyone who has repaired the exposed tendo achillis, even in a young healthy adult, well knows the risks entailed. I send this letter to The Journal so that drug manufacturers may be warned that carbolic solution in any drug is a potent agent at times, especially if it is used repeatedly. The circulation to the patient's legs is excellent for her age, and I can only blame the severe injury on the fact that phenol was in the medication. I have seen this phenomenon in fingertips and in facial lesions repeatedly treated with phenol, and I believe this drug should not be in lay hands.

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BETA-PROPIOLACTONE IS A CARCINOGEN

To the Editor:—The article by Allen and Murphy in The Journal, April 16, page 1759, on the use of beta-propiolactone for the sterilization of instruments and materials omits a very important consideration in the use of this substance. Beta-propiolactone is a carcinogen. Local sarcomas have been produced by subcutaneous injection of beta-propiolactone in rats (Walpole and others: *Brit. J. Pharmacol.* 9:306 [Sept.] 1954), and squamous papillomas and squamous carcinomas have been produced in mice by painting the skin with this material (Roe and Glendenning: *Brit. J. Cancer* 10:357 [June] 1956). In the laboratory of Dr. Paul Kotin we have produced sarcomas and squamous papillomas in mice by a single subcutaneous injection of a minute amount (.002 ml.) of beta-propiolactone (recent unpublished data). This information is brought to the attention of the readers of The Journal so that it may be more widely disseminated.

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BOOK REVIEWS

Back Pain: Diagnosis and Treatment Using Manipulative Techniques. By John McM. Mennell, M.D., Special Lecturer, Department of Physical Medicine, Medical School, College of Medical Evangelists, Los Angeles. Cloth. $9.50. Pp. 226, with 78 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; 25 Hollinger Rd., Toronto 16, Canada; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W. 1, England, 1960.

Undergraduate or graduate physicians, particularly those who undergo training in orthopedics, have ample opportunity to learn operative techniques. The effective use of therapeutic exercises is also a part of the armamentarium, but these physicians receive little or no instruction in the manipulative treatment of back pain. Most are satisfied to leave this therapeutic tool in the hands of osteopaths, chiropractors, and others who are not fully accredited. On the other hand, even though they may question the theoretical concepts and the clinical diagnoses made by manipulative therapists, physicians are aware that many patients attest to the therapeutic benefit produced by such treatment. I have an uneasy feeling that physicians are ignoring a potentially useful therapeutic tool. The author states that "the method [manipulation] has been extremely useful in relieving symptoms arising from any part of the spine which are not caused by herniated discs or other gross pathological processes." He supports the thesis that joint dysfunction [loss of movement] is the common cause of joint pain and that a diagnosis can be made and the lost movement restored by techniques which he describes in detail. Most orthopedists believe, on the other hand, that active exercises, carefully prescribed and faithfully pursued, will not only do what enthusiasts for manipulation claim for their methods but will also improve the muscle strength and the patient's posture, which are little affected by manipulation.

The ultimate test of any treatment method is its use, under controlled conditions and with critical observation. It is hoped that physicians who treat patients with backaches will read this excellent book and will try the techniques recommended. Proof of the author's theories will be hard to obtain. The overly enthusiastic physician and the hopeful patient with a self-limited disease may erroneously attribute success to manipulative techniques. The skeptical, scientifically trained physician will accept the claims for manipulative treatment of backache only if these are accompanied by an adequate statistical analysis of results of study. Such a study has yet to be made.

JOSEPH S. BARR, M.D.

Problems in the Evaluation of Carcinogenic Hazard from Use of Food Additive. Food Protection Committee, Food and Nutrition Board. Publication 749, National Academy of Sciences–National Research Council. Paper. $1. Pp. 44, with 5 illustrations. National Academy of Sciences-National Research Council, 2101 Constitution Ave., Washington 25, D. C., 1960.

The difficulties of determining the carcinogenic activity of a substance for man are recognized for the most part in a general way. This brief and well-written booklet might be read with benefit by all physicians who wish to understand some of the specific reasons for the difficulties.

The text briefly discusses terminology and definitions, strong and weak carcinogens, and general principles, such as comparative carcinogenicity (species and route of administration) and dose response. There follows a section on evaluation of the carcinogenicity of food additives in which are discussed the many problems involved in setting up adequate tests for carcinogenicity. These include brief and compact presentations on selection of species, sex and age of test animals, diet, dosage and dose response, use of control groups, character of the samples under test, group size and significance of results, routes of administration, pathological evaluation, and short-term test procedures. On the basis of the discussion, a practical procedure for evaluating carcinogenicity is presented.

Finally, there are brief statements concerning the statistical significance of accumulated data and the use of this information in drawing conclusions with respect to man. Pertinent charts, tables, and bibliography are included. Despite the title, the principles and difficulties discussed with respect to testing food additives as potential carcinogens can be applied to other agents concerned with carcinogenicity. In addition, many of the experimental problems presented in the use of test animals may well apply to the toxicity studies in general. It is strongly recommended that this brief booklet be read by all physicians.

WALTER WOLMAN, Ph.D.

Curriculum Development. By Amy Frances Brown, R.N., B.Ed., M.S. in N., Visiting Professor, Nazareth College, Louisville, Kentucky. Cloth. $10. Pp. 851, with 113 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1960.

This book is a detailed exposition of a curriculum for the education and training of nurses.

GLEN R. SHEPHERD, M.D.

QUESTIONS AND ANSWERS

PHANTOM PAIN

To the Editor:—*What is the current therapy of phantom pain after amputation? A 50-year-old man had an amputation of the leg about 1½ in. below the femoral neck for a rhabdomyosarcoma in the popliteal space 15 years ago. Since then he has had frequent phantom pains. What are the therapeutic possibilities?*

M. E. Arnold, M.D., Madisonville, Ky.

Answer.—Nearly every amputee has some phantom sensations, which are usually painless and clear up with time and use of the stump. Occasionally there is a patient in whom the pain persists and becomes more troublesome, especially when complicated by narcotic addiction. The treatment is controversial and remains unsettled. The bizarre sensory phenomena of the missing extremity suggest a functional disturbance. In a few cases reviewed by Kolb in "The Painful Phantom, Psychology, Physiology and Treatment" (Springfield, Ill., Charles C Thomas, Publisher, 1954) psychotherapy has been effective. In the opinion of most recent writers, the peculiar sensations must arise in the sensory cortex. It seems unlikely that they can come from a peripheral neuroma, since the phantom is never related to the distribution of any single nerve such as the ulnar, median, or sciatic. Instead, it principally involves the digits, possibly the entire hand or foot, but rarely any more proximal portion of the limb.

A priori, the most logical operation should be resection of the postcentral sensory cortex. Ablation of the first postcentral convolution has been tried and found wanting, probably because a much larger area is concerned in sensory perception. Excision of the entire cortex in which Penfield was able to evoke postural sensations on electrical stimulation is impractical, especially in the dominant hemisphere. Head and Holmes, however, reported a case in 1911 in which the pain disappeared after a contralateral middle cerebral thrombosis with widespread infarction of the parietal lobe. Pool and Bridges (*Bull. New York Acad. Med.* 30:302 [April] 1954) also relieved pain in the nondominant hemisphere by wide undercutting of the right parietal lobe up to the central sulcus. No further experiences with this procedure have been reported.

Frontal lobotomy has been resorted to in desperation, but only a limited amount of frontal white matter can be transected without producing permanent psychological deterioration. Newer methods by means of electrocoagulation in stages give promise of giving relief of otherwise intractable pain without serious psychological impairment, but results in phantom pain have not yet been recorded.

The best results with phantom pain have followed transection of the pain pathway in the opposite anterolateral column in the spinal cord. In the results reported by White and Sweet (*A.-M. A. Arch. Neurol. & Psychiat.* 67:315 [March] 1952) pain was relieved in all but 1 of 10 patients with lower extremity phantoms in which cordotomy was followed by an adequate level of analgesia. Pain recurred in two with later opening up of islands in which sensitivity to pinprick returned. This operation fails, however, to eliminate pain sensation completely in some 20% of persons, and after a year another 10 to 15% can again detect the prick of a pin. Whenever this occurs, the awareness of pain in the phantom returns.

To summarize, operations on the cortex carry only a slight chance of success and are associated with severe risk, especially that of setting up an epileptogenic focus. Cordotomy, despite a 33% chance of failure, carries little risk in expert hands and appears to be a far better procedure than frontal lobotomy. This can be considered if cordotomy fails and the patient is threatened with narcotic addiction or severe mental depression, provided one of the more recent conservative procedures is used.

HEMOLYTIC DISEASE OF FETUS AND NEWBORN INFANT

To the Editor:—*Can anything be done during pregnancy to lessen the severity of erythroblastosis in the fetus? An Rh-negative mother and an Rh-positive father have had one normal and one erythroblastotic child. The latter child received an exchange transfusion. Is the use of a citrus "bioflavonoid" compound of benefit in this situation?*

M.D., Indiana.

Answer.—There is no medicament which, when given to an Rh-negative mother who has been sensitized against the Rh blood factor and has had one erythroblastotic child, will lessen the severity of erythroblastosis in the fetus. All attempts at prevention or modification of such sensitization have been futile. Originally, almost 20 years ago, when the Rh etiology for erythroblastosis was first discovered, administration of large doses of vitamin C was advised "to help preserve the integrity of the placental barrier," without the slightest evidence of subsequent benefit. Since then a variety of trials have been advocated, and all have proved unsuccessful. These include injection of a highly dilute

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

solution of ethylene disulfonate, theoretically supposed to minimize the effects of antibody-antigen combination; "Rh hapten," an ether extract of blood cells, supposedly containing the Rh substance in nonantigenic form, for the avowed purpose of "neutralizing" maternal Rh antibodies; methionine, to protect the liver and diminish the possibility that liver damage could produce kernicterus; cortisone and ACTH, for their supposed beneficial effect on antibodies; and repeated injections of pertussis vaccine, given on the theoretical basis that there might be a "competition of antigens" interfering with formation of Rh antibodies. Most recently, the use of flavonoids was advised for the same possible reason as the earlier trial of vitamin C, namely, "to strengthen" the placental barrier. Again, there has been no evidence of help from this. The difficulty in evaluation of possible therapeutic benefit from any medicament is the normal wide variation in the severity of hemolytic disease of the fetus and newborn infant, even with comparable antibody titers in different women. The fluctuations in antibody titers in any sensitized person, the differences in infants even when born to the same mother, and other such variable conditions all must be known to the observer, and the statistical proof must be beyond probability errors. For example, the probability of a second stillbirth in a sensitized woman is about 70%. If, with the use of a drug, one could apparently lower this figure to 40% in a dozen cases it would seem like a worthwhile treatment. In fact, however, it would require over four times as many such successful results, 50 or more, to prove statistical significance.

At the time of writing, the only successful approach to diminishing the severity of hemolytic disease of the fetus and saving a putatively stillborn infant is to deliver it at a reasonable interval before term, judging each situation on its own merits.

Reference

Allen, F. H., and Diamond, L. K.: Erythroblastosis Fetalis, Including Exchange Transfusion Technic, Boston, Little Brown & Co., 1958, chap. 9.

EATING AND SWIMMING

To the Editor:—*It has been and still is commonly being taught that a period of at least one hour should elapse after eating before swimming. Is there any factual, statistical, or physiological basis for this teaching?*

W. K. Cooper, M.D., Cedar Rapids, Iowa.

Answer.—Such precautionary recommendations have been based on the premises that the active exercise of swimming interferes with digestion, and that cramps in swimmers are more prevalent after meals than at other times. Studies, in which the stomachs of persons who swam and of others who were inactive were pumped at corresponding periods after they had eaten the same meals, do not show significant differences in the extent of digestion between the two groups. Neither do records of the occurrence of cramps prove that they are more likely to take place after meals than otherwise.

That psychic factors do affect the digestive process, is well known, however. Where there is an emotional element involved, such as competition, fear of water, or some similar influence, digestion may be slowed or "upset." Hence, since there will ordinarily be persons so affected in any group, prohibition of swimming immediately after meals is probably a wise rule for schools and similar institutions. For the individual person it is a matter of personal reactions and practice.

SUICIDE ATTEMPT WITH COOKING GAS

To the Editor:—*A patient attempted suicide by opening the kitchen oven gas jets for about 25 minutes. What is the effect of prolonged exposure to illuminating gas on cerebral tissue? What would be the resulting symptoms and psychiatric findings? What would the prognosis be?*

Eugene J. Audi, M.D., Glen Rock, N. J.

Answer.—Carbon monoxide (CO) is the principal constituent of illuminating gas, and the toxic effects are due to the stable combination of carbon monoxide with hemoglobin, thus producing an anoxemia. This leads to death of some nerve cells. The time of exposure necessary for severe nervous tissue damage depends on the concentration of CO, which in this case apparently was over 20%, with about 20% methane gas. Since the patient was found unconscious, the blood saturation level may have been about 50% and severe symptoms should have followed, such as headache, giddiness, impaired mental power, and a psychosis.

The immediate effects of CO poisoning are headache and vomiting. After the initial symptoms, there may be a stage of apparently complete recovery followed by severe and persistent symptoms. In the chronic stage, there are both neurological and mental symptoms and one or the other may predominate. The mental symptoms are apathy, lack of initiative, and indifference to duties and responsibilities. Some patients continue to show confusion, bewilderment, and impairment of memory accompanied by the type of hallucinations found in polyneuritic psychosis. Amnesia lasting six to nine months may occur. In extreme cases, the patient sinks to the level of vegetative existence with incontinence, unresponsiveness, and inability to carry on any voluntary activity. Occasionally a patient suffers from auditory aphasia. Lesions have been recorded in every part of the nervous system and are usually diffuse, but neurological symptoms are usually due to degenerative changes in the putamen or globus pallidus. Frequently, therefore, there is a modified type of paralysis agitans, with stiffness of the extremities caused by muscular hypertonia. The condition of many patients with mental sequelae of CO poisoning begins to improve within a few weeks after exposure and they recover completely within two years. Those who have not recovered within that period remain in a state of mild or severe mental enfeeblement.

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Dutra, F. R.: Cerebral Residual of Acute Carbon Monoxide Poisoning, Am. J. Clin. Path. **22**:925-935 (Oct.) 1952.

Katz, M.: Carbon Monoxide Asphyxia, Common Clinical Entity, Canad. M. A. J. **78**:182 (Feb. 1) 1958.

PROCAINE HYDROCHLORIDE AND AGING

To the Editor:—*I have recently seen references, in a few medical journals but more often in popular magazines, regarding the use of procaine hydrochloride injections (administered intramuscularly, intravenously, and even intra-arterially) for the management of arthritis, osteoporosis, graying of hair, senility, and other conditions. The references all seem to be of Rumanian and Russian origin. Have there been any qualified reports of similar findings in either the American or the British medical press?*

Milton M. Greenberg, M.D., Brooklyn, N. Y.

Answer.—Dr. Henry Beecher of the Massachusetts General Hospital did extensive work with this type of injection some years ago. Some patients had severe untoward results, and for those who noticed improvement after receiving this type of therapy, the improvement approximately equalled that obtained from moderate doses of aspirin.

Editor's Note: A list of references on this subject appears below. None of the articles claim that the treatment is beneficial.

1. Research on Novocain Therapy in Old Age, English translation of seven papers by Anna Aslan and coworkers; C. I. Parhon, C. David, M. Bürger, F. H. Schulz, U. Köhler, and F. Manpel, originally published in German in Die Therapiewoche in 1956-1957. Published by Consultants Bureau, Inc., New York, 1959, 72 pages, $12.50. (Reviewed in *J. Gerontol.* **14**:450 [Oct.] 1959.) 2. Russian and Iron Curtain Proposals for Geriatric Therapy [Current Comment], C. D. Leake, *Geriatrics* **14**:670 (Oct.) 1959. 3. Procain and the Aging Process, M.D., **3**:68 (Nov.) 1959. 4. Uses of Procaine, Information Please, *G. P.* **19**:174 (March) 1959. 5. Rejuvenation, editorial, *Canad. M. A. J.* **82**:26 (Jan. 2) 1960. 6. "H3," editorial, *Brit. M. J.* pp. 1163-1164, Nov. 28, 1959.

YELLOW JACKET STING

To the Editor:—*In* The Journal, *May 30, 1959, page 632, there was an answer to a question concerning a near-fatal reaction to an insect sting. The Committee on Allergy of the Academy of Pediatrics believes that the answer did not include all the pertinent information on such reactions and that physicians should be informed of recent developments on this important subject contained in a report from the Committee.*

The statistical study by Parrish (A.M.A. Arch. Int. Med. 204:*198 [Aug.] 1959) and the experience of others (Mueller,* New England J. Med. *261:374 [Aug.] 1959) indicate that allergic reactions to insect stings probably occur more frequently than is supposed. Occasionally such a reaction may account for some of the unexplained deaths in the insect seasons which are usually attributed to cardiac failure or heat prostration. Physicians should be alert to this possibility.*

Increasing sensitivity usually follows a sting which produced a systemic reaction, and this hypersensitivity apparently does not diminish spontaneously over periods as long as 20 years. Occasionally patients have reported the development of immunity after a reaction sting, but single or multiple cross sensitivity can occur and this supposed immunity cannot be relied on, for it depends on identification of the insect causing both the reaction sting and subsequent nonreaction stings. Such identification is extremely unreliable.

Desensitization with bee and wasp extracts was successfully accomplished as far back as 1930 by Benson and subsequently by many others. Every patient with a systemic reaction to these insect stings should have the potential dangers of a subsequent sting explained to them and be advised to have desensitization treatment with a mixed bee and wasp extract. This sensitivity may be extreme, and great care must be taken in testing and treating these patients. Reports published over the past 10 years have uniformly indicated protection for practically all patients receiving stings subsequent to desensitization. No deaths from stings have been reported in properly treated patients. There have been instances, however, when fatal reactions occurred because physicians had told patients that there was nothing but expectant treatment for their hypersensitivity.

Acute sting reactions should be treated with liberal doses of epinephrine. Steroids, given by any route, act too slowly to be of value in the immediate anaphylactic reaction. Patients under treatment should carry sublingual tablets of isoproterenol hydrochloride until a subsequent sting without reaction has demonstrated they no longer need such protection. Epinephrine and a syringe for use by the patient is not recommended as the sole protection because the equipment is frequently unavailable or not operable when needed, or reaction may be so rapid that the patient will be unable to prepare and give himself the injection. Although local applications of cold may contribute to comfort, the only important local treatment is the proximal application of a tourniquet, if the sting is on an extremity.

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ABSTRACTS FROM THE LITERATURE

A. M. A. Archives of Surgery

81:1-172 (July) 1960

Surgical Lesions of the Biliary Tract
W. Walters ....p. 1
Malignant Thyroid Adenoma
J. W. Welch, V. E. Chesky, and C. A. Hellwig ....p. 14
New Trocar Designed for Insertion of Foley Catheter
A. Hurwitz ....p. 24
Surgical Results in Patients with Cardiac Septal Defects
J. L. Ehrenhaft, E. O. Theilen, and others ....p. 26
Meckel's Diverticulum
W. S. Moskovitz, C. W. Hughes, and W. F. Bowers ....p. 36
Jejunal Diverticulum with Inflammation and Peritonitis
N. Kubota and S. L. Yee ....p. 45
Functioning Islet Cell Adenoma of the Pancreas
A. W. Ulin, P. Martinez, and R. Greenstein ....p. 50
Auriculovenous Hemodialysis
C. E. Murdock Jr. ....p. 53
Effect of Venoarterial Bypass on Coronary Blood Flow
J. E. Connolly, M. B. Bacaner, and others ....p. 58
Spontaneous Arteriovenous Fistula
J. R. Thistlethwaite, R. K. Hughes, and others ....p. 61
Aortic-Femoral Graft 7 years After Iliac Artery Ligation
G. I. Thomas ....p. 65
Nonpalpable Epigastric Hernias
R. N. Brown ....p. 69
Esophageal Hiatal Hernia
R. P. McBurney ....p. 72
Thoracolumbar Sympathectomy for Essential Hypertension
S. I. Schwartz, P. D. Harris, and others ....p. 76
Portal Hypertension in Myeloid Metaplasia
N. Oishi, S. N. Swisher, and others ....p. 80
Intestinal Polyps and Peutz-Jegher's Syndrome
M. J. Allen and J. E. Hershey ....p. 87
Superior Mesenteric Arterial Embolectomy
D. S. Saris and J. F. Uricchio ....p. 90
Intermittent Claudication Studied by Electromyography
J. D. Griffiths, G. de Takats, and J. Frost ....p. 94
Complications of Temporary Tube Gastrostomy
K. L. Senter ....p. 103
Reticulum Cell Sarcoma of a Rib
A. Lambert and A. P. Stout ....p. 107
Recurrence of Adenocarcinoma of Rectum
J. Sonneland ....p. 112
Ventricular Myocardium
A. R. Dobell, F. R. Sanchez, and D. R. Murphy ....p. 118
Cardiac Output and Posture in Arteriovenous Fistulas
M. B. Leslie, B. A. Portin, and W. G. Schenk Jr. ....p. 123
Antibiotics and Mortality from Liver Autolysis
M. J. Orloff and G. W. Peskin ....p. 129
Autogenous Vein Grafts and Teflon Grafts
R. R. Bradhem and D. B. Nunn ....p. 136
Villous Papilloma of Rectum and Electrolyte Losses
I. Rudman, C. Otto, and O. J. Novota ....p. 140
Costal Intraosseous Venography in Portal Hypertension
R. Schobinger and others ....p. 143
Clinical Use of Frozen Red Cells
J. L. Tullis, L. L. Haynes, and others ....p. 151
Conservative Treatment of Certain Fractures in the Hand
P. J. Burnham ....p. 155

Surgical Lesions of the Biliary Tract.—The author reviews his 35 years' experience in the management of surgical lesions of the biliary tract, traces the influence of the physiologic and chemical disturbances resulting from infection and obstruction of the extrahepatic and intrahepatic biliary tract. Reference is made to researches he carried out during his fellowship and their application to clinical practice. Clinical studies of patients with complicated lesions of the biliary tract and methods of treatment are described.

The author's experience with 571 operations on 445 patients with strictures of the common and hepatic bile ducts, who were followed up for 5 to 25 years, indicates that excellent or good results were obtained by 75% of the patients. There were 24 women who, following operations for strictures of the ducts, had 34 pregnancies resulting in 29 live births.

Malignant Thyroid Adenoma.—To ascertain if the grade of differentiation was a determinative factor in the clinical course of malignant thyroid adenomas, a 15-year survey of over 3,000 thyroidectomies was undertaken. Two hundred sixty-six cases of thyroid cancer were divided into 2 groups on the basis of the survival rate and the natural history of the tumor. One hundred fifty-six adenomas satisfied the dual criteria of being both solitary and a group 1 type of malignancy (well differentiated with favorable prognosis). Treatment consisted of either a total lobectomy or a combination of total and subtotal lobectomy with few modified neck dissections and no resort to x-ray or radioactive iodine as adjuvant therapy. With a 12-year follow-up of 88% of the patients, the survival rate exceeded 90% and the apparent cure rate was 85%.

Trocar Designed for Insertion of Foley Catheter.—A new trocar has been designed with a bipartite outer sleeve to allow easy and safe insertion of a Foley catheter into the pleural space or into the urinary bladder. The trocars come in 2 sizes. The smaller trocar will accommodate an 18 F. Foley catheter and the larger one a 26 F. Foley catheter.

Meckel's Diverticulum.—Meckel's diverticulum, found in 2% of autopsies, may cause intestinal obstruction, intussusception, hemorrhage or perforation. It may contain aberrant gastric mucosa, pancreatic tissue or carcinoid tumor. There may be acute diverticulitis, usually diagnosed as appendicitis, or a congenital enteric fistula may be present. In 20 patients from 3 months to 35 years old, 16 were males and, in the group, all the above complications were seen. One patient showed acute diverticulitis, perforation, abscess formation, intestinal obstruction, aberrant gastric mucosa, and carcinoid tumor. Because of the severity of complications, search for Meckel's diverticulum always should accompany laparotomy unless definitely contraindicated and excision should be done if good surgical judgment permits.

Auriculovenous Hemodialysis.—The author is concerned with the surgical-technical aspects of linkage of a patient to an artificial kidney. The value of right atrial outflow in conjunction with left common iliac venous inflow for the majority of cases is indicated by experience with the method in 6 dialyses in 3 patients, (now 8 dialyses in 5 patients). The portal of entry for each cannula is the sapheno-femoral venous juncture.

Functioning Islet Cell Adenoma of the Pancreas.—Clinical and technical points in the surgery of islet cell tumor of the pancreas are presented. These tumors are small, may be nonfunctioning, are malignant in over 10%, and are multiple or ectopic in over 12% of cases reported. Consequently, a direct approach by mobilizing the pancreas and by resection has merit. The tumor is more easily discerned, malignancy is better handled than with local excision. The operative mortality is generally 9% with either procedure, whether radical resection or local excision. However, the Mayo Clinic reported that the complication of fistula was less (9 out of 26 patients as compared with 20 out of 48), mortality was less (1 out of 26 as compared with 4 out of 48), and cure rate was significantly higher with subtotal pancreatectomy. If no tumor was seen, subtotal pancreatectomy cured 75% of patients considered. Of the large percentage of cases reviewed in which no tumor was found, one third were later found to have tumor at operation or autopsy. With the exception of tumor of the pancreatic head, partial or subtotal pancreatic resection is the procedure of choice.

Spontaneous Arteriovenous Fistula.—In a 63-year-old man, anuric for 24 hours, an abdominal aortic aneurysm was resected and replaced by a Teflon graft. A fistulous opening into the inferior vena cava was closed. Postoperatively, normal urinary output was resumed immediately.

Three months later, an emergency operation was performed for massive upper gastrointestinal bleeding. A fistula between the upper aortic suture line and the duodenum was closed and a longer Teflon aortic graft inserted. The patient died in irreversible shock. The anuria was apparently due to inadequate renal blood flow secondary to the large arteriovenous fistula. Multiple abscesses were found in the excised aneurysm, suggesting that infection was the cause of the aortic-duodenal fistula. Spontaneous aorto-vena caval fistula is a rare lesion. To our knowledge, this is the 1st reported case presenting with complete anuria.

Nonpalpable Epigastric Hernias.—Nonpalpable epigastric hernias occur in the linea alba or the posterior rectus sheath above the umbilicus. Onset may follow coughing. Pain is localized to a nickle-sized area, may be aggravated by lying down, but is not associated with food. Preoperative gastrointestinal x-ray studies are indicated.

A 3 to 5 mm. defect in the posterior rectus sheath through which a small vessel traversed was found in 4 cases. A little piece of properitoneal fat accompanied the vessel. Repair was accomplished by cutting and ligating the vessel, allowing the fat to retract through the defect, then closing the defect with 1 or 2 nonabsorbable sutures. Thorough exploration of the abdominal wall and viscera should be done. More than 1 defect may exist and should not be overlooked.

Thoracolumbar Sympathectomy for Essential Hypertension.—The long-term effects of thoracolumbar sympathectomy were evaluated in series of 90 hypertensive patients. The majority of patients did not achieve either a persistent decrease of diastolic pressure or relief of symptoms. A small but significant percentage of patients demonstrated a dramatic and continued decrease in blood pressure and improvement of symptoms subsequent to surgery. The lack of predictability of surgical response was emphasized, and the limited value of both the sodium amytal and spinal anesthesia tests was demonstrated.

Esophageal Hiatal Hernia.—Sixty-nine cases of surgically repaired hiatal hernias were studied to compare the Allison technique with repairs done before the adoption of the Allison principle.

In 21 cases using the lateral repair, there were 11 recurrences during a follow-up period of 2 to 13 years. In 48 cases in which the Allison technique was used, no proved recurrences were present in a 6-month to 5-year follow-up. Two cases in the group, however, are suspected of having recurrences, but the recurrences have not been demonstrated yet. The improved results have led to broadened indications for surgery, and concomitant abdominal procedures have repeatedly been carried out along with hernia repair. There was 1 postoperative death in the entire series. The abdominal approach is preferred except in cases of obesity or in recurrent hiatal hernia repair.

Portal Hypertension in Myeloid Metaplasia.—Additional support for the thesis that increased forward blood flow through the splenoportal system may be a factor in the pathogenesis of portal hypertension is offered. A patient with myeloid metaplasia, who demonstrated portal hypertension with bleeding esophageal varices in the absence of portal obstruction is presented. The increase in portal venous blood that would be necessary to raise portal pressure to the levels encountered clinically is calculated on theoretical grounds. Although the patient presented was successfully treated with a portacaval shunt, the surgical approach indicated for this unusual type of portal hypertension remains unresolved.

Intestinal Polyps and Peutz-Jegher's Syndrome.—The syndrome of small intestinal polyposis associated with melanin spots of the oral mucosa, lips, and digits has rarely been surgically treated. Inasmuch as the area of polyp formation is not localized, surgical resection of all involved segments of bowel is impossible. Dormandy's studies of Peutz-Jegher's syndrome, in 1957, have cast doubt on the probability of malignant transformation of the polyps in this disease. Surgical intervention was indicated in our patient because of recurrent gastrointestinal hemorrhage and partial small bowel obstruction. Surgical management consisted of everting segments of bowel through multiple enterostomies, excising the larger polyps, fulguration of the smaller polyps with the electrosurgical unit, and removal of an obstructing mass of polyps at the ileocecal valve by a right hemicolectomy. In the 32 months since surgery, the patient has been relieved of significant bleeding and obstructive symptoms.

Intermittent Claudication Studied by Electromyography.—The response of muscle to exercise and its relation to intermittent claudication was studied in 80 limbs of 40 subjects. Electromyographic tracings were correlated with bloodflows determined by a recording oscillometer. In healthy subjects, there is an increased amplitude of muscle contractions associated with an increased bloodflow when muscles are stimulated. When there is decreased amplitude on stimulation, bloodflow decreases. In certain cases, there is a diminished amplitude of muscle contractions, but an increase in bloodflow. The disease here is in the smaller vessels such as may occur in the atherosclerosis of diabetes. Four types of ergomyographic tracings correspond to the 4 clinical grades of claudication. Thus, a subjective symptom has been objectively recorded. The effect of lumbar sympathectomy, of direct arterial surgery, and of the value of voluntary and involuntary exercise has thus been registered.

Superior Mesenteric Arterial Embolectomy.—Acute occlusion of the superior mesenteric artery is not readily appreciated by the physician because collateral circulation permits a brief period of adequate blood supply and a temporary absence of abnormal physical signs in the abdomen. The 1st successful mesenteric arterial embolectomy without resection of intestine was reported by Shaw in 1957. A 2nd patient presented by the authors, and a review of the literature demonstrate that any cardiac patient with acute abdominal pain, vomiting, and a rapidly rising leukocytosis despite an inconspicuous abdomen must be considered for exploration for acute mesenteric arterial occlusion. Waiting for the usual signs of an acute abdomen before exploration, has been precisely the reason for massive resections of infarcted bowel and a high mortality. Earlier surgery should increase the chance for successful embolectomy.

Complications of Temporary Tube Gastrostomy.—Fifty-seven cases of gastrostomy performed at The California Lutheran Hospital in the period 1952 to 1958 were reviewed. Fifty of these consisted of temporary tube gastrostomy and were studied concerning the incidence of complications. Three patients died as a direct or indirect result of tube gastrostomy. Complications were as follows: (1) failure of the gastrocutaneous defect to close following tube removal; (2) massive fatal peritonitis secondary to leakage from the gastrostomy site; (3) gastrocutaneous fistula complicating a left subdiaphragmatic abscess. Careful suture approximation of apposing peritoneal surfaces at the gastrostomy site, use of a small (#14 or #16) tube, extubation after 7 days (with the stomach empty), care that the gastrostomy site is not disturbed should wound dehiscence occur, and avoiding of gastrostomy when poor wound healing is anticipated were believed important in minimizing complications.

Recurrence of Adenocarcinoma of Rectum.—Recurrence of rectal adenocarcinoma may be delayed for years, as demonstrated by this report of a 73-year-old woman with a 17 year interval between an abdominoperineal resection and recurrence near the colostomy. Although recurrence of tumor in the incision is well documented in the article's cited literature, most such recurrences occur within months or at best a few years of the primary surgery. Factors influencing the 17-year latent period were undoubtedly a most unusual tumor-host relationship combined with radiosensitivity of the tumor. Radiosensitivity of colorectal carcinoma has been increasingly reported. The cancer implant had been exposed to heavy radiation during treatment of cervical carcinoma arising 5 years after the abdominoperineal resection. Of further interest in this case are the facts that she developed jejunal obstruction 9 years after radiation therapy and that a 3rd primary carcinoma developed in the urinary bladder.

Reticulum Cell Sarcoma of a Rib.—This 18-year surgical cure of a reticulum cell sarcoma of the chest wall, arising primarily in a rib, is unique in that it represents the only case of long-term, symptom-free survival of a patient with such a tumor. This is in part due to the rarity of this disease but mainly to the surgery that was performed, which was largely responsible for cure. The factors in the surgical technique that are considered important are emphasized, along with an analysis of the problem of chest wall sarcoma of both soft tissue and bone as classified in the literature to date.

Autogenous Vein Grafts and Teflon Grafts.—The purpose of this study was to determine on a comparative basis the merits of autogenous veins and braided crimped Teflon tubes as substitutes for arteries with external diameters 5 mm. or less. These grafts, measuring 25 mm. in length and 4.5 mm. in external diameter, were used to bridge a 20 mm. defect in femoral arteries of dogs. Patency of the grafts was followed by aortography. The animals were sacrificed when the graft became occluded or at 6 months postoperative. Seven of 15 vein grafts and 5 of 10 Teflon grafts remained patent. Even though the occlusion rate was the same, Teflon was preferred because of its ready availability and greater ease of handling.

Ivalon as Replacement for Right Ventricular Myocardium.—This study was undertaken because of the need for a prosthesis to enlarge the right ventricular outflow tract in many patients with the tetralogy of Fallot. A standard sized prosthesis of polyvinyl alcohol (Ivalon) sponge was used to replace an excised full-thickness portion of the anterior wall of the right ventricle in 15 dogs. Both compressed and uncompressed prostheses were used. The animals were sacrificed from 26 to 405 days after operation, at which time the prostheses were found to be uniformly stony hard. Microscopic examination showed marked fibrous tissue invasion with fibrocartilage visible in 5 prostheses, 2 of which also showed calcification. From this experimental study we concluded that Ivalon possessed qualities which make it undesirable as a prosthesis for the right ventricular outflow tract.

Cardiac Output and Posture in Arteriovenous Fistulas.—This study in the dog was designed to (1) quantitate the relationship between total fistula flow and increased cardiac output and (2) demonstrate the effects of posture variation upon fistula flow. Such information was desired since it has previously been reported that cardiac output in acute fistulas cannot increase enough to compensate for fistula flow and reduced flow must occur in other parts of the body. Effect of total body tilt on cardiac output and fistula flow was investigated because of reports of alteration in flow following such postural change. The results indicated that total fistula flow representing up to 40% of control cardiac output was compensated for by an equivalent increment in left ventricular output. Total body tilt produced cardiac output alterations; but fistula flow changes seemed to be merely a reflection of this output change.

Antibiotics and Mortality from Liver Autolysis.—To determine whether bacteria are of importance in liver autolysis, studies were performed upon 40 dogs treated with a variety of antibacterial drugs before and after devitalized liver was placed intraperitoneally. All control dogs, those treated with oral neomycin and succinyl sulfathiazole and 80% of those treated with parenteral streptomycin, died with hemorrhagic peritonitis. Treatment with parenteral penicillin and either oral or parenteral oxytetracycline resulted in survival of all animals. However, these effective agents failed to alter consistently the flora of the liver, gastrointestinal tract, and peritoneum, which suggests that their efficacy may result from reduction of the total number of bacteria rather than from a specific influence on any one type of organism. It appears that the pathological phenomena result from the lytic action of bacteria on devitalized tissue with formation of noxious breakdown products.

Villous Papilloma of the Rectum and Electrolyte Losses.—Although villous papilloma of the rectum ordinarily offers little difficulty in management, rarely this tumor can produce a perplexing and life-threatening clinical syndrome. In this case the presenting symptoms were not alarming although the villous growth covered 150 sq. cm. of rectal surface. Despite this unusual size, the tumor was difficult to identify through the sigmoidoscope because of its gross resemblance to normal mucosa. The secretory surface of the papilloma unexpectedly began to produce huge quantities of fluids containing electrolytes at a rate which resisted all efforts at replacement. Consequently the authors were compelled to resect the tumor in the face of a persisting electrolyte deficit. The patient failed to recover. This case illustrates that villous papilloma of the rectum can create an urgent clinical problem which requires swift diagnosis and immediate therapy.

Surgical Results in Cardiac Septal Defects.—The mortality in the surgical treatment of 231 patients with atrial and ventricular septal defects was 10% for the entire group. All the deaths occurred in patients who had complicated defects or grossly abnormal physiologic changes such as pulmonary hypertension. Patients with atrial lesions were operated on using hypothermia alone. Valvular pulmonic stenosis or partial anomalous pulmonary venous connections did not increase the hazard of the procedures. Death in the hypothermia group results from early attempts to repair ostium primum defects. It also resulted in some patients with pulmonary hypertension. One hundred thirty-three patients with ventricular septal defects have been operated upon using the pump oxygenator. All the patients with isolated and uncomplicated defects survived. Factors related to the increased morbidity and mortality were the length of perfusion, insertion of plastic prosthesis, rhythm disturbances, postoperative respiratory complications and, occasionally, cerebral or coronary air embolization.

Veno-Arterial Bypass and Coronary Blood Flow.—In previous writings the authors described a simple unoxygenated veno-arterial bypass for the support of the circulation in the failing heart. Experiments in the dog uniformly showed a remarkable return of cardiac function, with significant increases in the cardiac output, when the bypass was instituted in the face of a fixed cardiac overload. The improvement in cardiac function seemed to be directly related to an increase in aortic root pressure. This elevated root pressure resulted in an increase in coronary blood flow which in turn was responsible for the observed cardiac improvement. Coronary blood flow has been measured by a myocardial washout of Na_{24} and by direct cannulation of the coronary sinus in 9 dogs. Coronary blood flow, as measured by these 2 techniques, uniformly fell to low levels with pulmonary artery constriction, and it increased remarkably with veno-arterial bypass. It appears, then, that acute right ventricular failure can be in part controlled by restoring the aortic root volume and pressure by mechanical means.

A. M. A. Archives of Neurology

3:1-97 (July) 1960

Cutaneous Reflex Changes in Development and Aging
J. W. Magladery and others. .... p. 1
Fusimotor Nerve Function in Man.
W. M. Landau, R. A. Weaver, and T. F. Hornbein. .... p. 10
Neural Limitations of Visual Excitability
W. S. Battersby and others. .... p. 24
Proteolytic Enzyme from Cat Brain During Stimulation
L. F. Chapman and others. .... p. 43
Focal Cortical Cerebellar Sclerosis
L. C. McHenry Jr., J. M. Foley, and O. S. M. Marin. .... p. 46
Human Subjects Living in "Slow Rotation Room" for 2 Days
A. Graybiel, B. Clark, and J. J. Zarriello. .... p. 55
Hippocampal Slow Waves
W. R. Adey, C. W. Dunlop, and C. E. Hendrix. .... p. 74
Neurological Eponyms
H. S. Barrows. .... p. 91

Cutaneous Reflex Changes in Development and Aging.—Latencies of clinically elicited cutaneous reflexes—superficial, abdominal, and plantar—have been compared in normal persons of various age groups with simple reaction times and with similar reflexes evoked by electrical stimuli to skin. During development all responses were found to be slow, becoming progressively more rapid until adolescence when adult values were reached. In elderly persons, though reaction times and electrically evoked reflexes were little altered, clinical reflex latencies were greatly increased. Relevance of these latency differences to motor activity in maturation and aging are discussed.

Fusimotor Nerve Function in Man.—In 10 normal volunteers, in 11 patients with parkinsonian rigidity, and in 11 subjects with severe spasticity, graded doses of local anesthetic were injected intrathecally or extradurally in the lumbar region. This procedure blocked the small-diameter (gamma) fusimotor fibers along with the fine sensory fibers (pain and temperature), but spared the motor efferent and large afferent axons. The consequent depression of muscle-spindle stretch-receptor excitability decreased both tendon reflexes and pathological hypertonia, while strength was relatively spared. The hypotonia thus produced was not associated with ataxia or proprioceptive deficiency. Fusimotor function is essential for the maintenance of muscle tone and stretch reflexes, but there is no evidence that fusimotor activity is pathologically increased in spasticity or rigidity, or decreased in cerebellar disease.

Neural Limitations of Visual Excitability.—Changes in the visual threshold over time (visual excitability) were measured in 40 patients with lesions of the nervous system by means of "test" and "conditioning" light flashes presented at varying intervals. When these flashes were successively directed into the same eye (monocular stimulation) the patients with bitemporal field defects and also those with homonymous field defects showed marked decrements in visual excitability. When the flashes were presented to different eyes (binocular stimulation) only patients with homonymous field defects manifested marked deficits. In both instances, however, long-lasting deficits in visual excitability were readily demonstrable in portions of the field which appeared "spared" upon campimetry. These findings confirm predictions made from prior studies on normal subjects, and they support the concept of a diffuse representation of function within the cerebral visual system.

Proteolytic Enzyme from Cat Brain During Stimulation.—Certain proteolytic enzymes when incubated with plasma globulin form vasodilator polypeptides that can be assayed in minute amounts. Cats were prepared for acute perfusion of the cerebral ventricles and subarachnoid space by placement of 1 polyethylene canula in a lateral ventricle and another in the cisterna magna. Perfusate was assayed, before and after incubation with globulin, for the capacity to contract isolated rat uterus, to relax rat duodenum, and to depress rat arterial blood pressure. Protease activity was inferred from the formation of an hypotensive polypeptide during incubation with globulin. A significant transient increase of this protease was observed predictably following brief electrical stimulation of the brain. The observed hypotensive action of perfusate-globulin mixtures suggests that local polypeptide formation by brain protease is an important determinant of vasomotor activity in the brain.

Focal Cortical Cerebellar Sclerosis.—Four pathological studies of focal cortical cerebellar sclerosis, along with a survey of the literature, show that this lesion is a chance postmortem finding characterized grossly by circumscribed depressed or atrophic areas usually in the superior, lateral, and posterior aspects of the cerebellar hemisphere. The lesion is asymptomatic and its cause is unknown. It may be associated with almost any disease. Focal cortical cerebellar sclerosis is differentiated from other cerebellar lesions by its histological features. There is a marked loss of all parenchymatous elements in the Purkinje, granular and molecular layers of the cerebellar cortex and of the myelin and axis cylinders of the underlying white matter with a proliferation of fibrous astrocytes in all areas, particularly in the Bergmann layer. Secondary atrophy is present in those areas of the olive which project to the involved cerebellar cortex.

Human Subjects in "Slow Rotation Room" for 2 Days.—The dual purpose of this report was to describe a unique procedure for stimulating the reticular formation, and the symptoms provoked in man. The subjects were exposed to constant rotation at different speeds in a closed room provided with laboratory facilities and living accommodations. The effective stimulus was the bizarre aperiodic excitation of the semicircular canals on movement of the head out of the plane of rotation of the room. One subject without labyrinthine function felt well under all experimental conditions. The symptomatology varied in healthy subjects and included anxiety, sleepiness, sweating, oliguria, visual illusions, and gastrointestinal disturbances. Some symptoms persisted long after the stimulus ceased. Adaptation was a prominent feature, as were aftereffects on cessation of rotation. The usefulness of the procedure in studying the functions of the reticular formation and certain psychophysiological mechanisms was emphasized.

Hippocampal Slow Waves.—Distribution and behavioral correlates of slow-wave trains in various parts of the hippocampal system have been examined during approach training in cats with implanted electrodes. In naive animals, in the absence of a conditioning stimulus, irregular slow-wave trains occurred over a wide spectrum of 4 to 7 waves per second, and were synchronized in dorsal and ventral hippocampus. During initial presentations of conditioning stimuli, a burst of rhythmic slow-waves at 5 to 6 waves per second appeared, and was rapidly restricted on successive trials to dorsal hippocampus and entorhinal area, persisting without adaptation throughout training. These bursts were related to locomotion towards a goal, rather than to Pavlovian orientation. Electronic computing of autocorrelation and cross-correlation functions of slow-wave trains has confirmed their inherent rhythmicity and shown clear differences between untrained and trained animals in phase relationships of these trains in various hippocampal zones.

Neurological Eponyms.—Since the use of neurological eponyms is frequently decried, over 450 neurological eponyms were culled from the literature to estimate the extent and nature of this habit. In addition, a small survey of their use in an area producing neurologists was analyzed. The eponym's most valuable function is to provide a simple label for complex phenomena. Despite this, the facts described in this study indicate that the use of eponyms is harmful. The redundancy of eponyms, coupled with the marked variations in their definitions, hampers communication. The neurologist's use of the eponym has little bearing on his judgment of its value. He uses it only on the basis of familiarity. The need for the eponym is of a bygone era in neurology. It is an ill-suited tool today.

Acta endocrinologica, Copenhagen

33:317-476 (March) 1960. Partial Index

Tetanic Syndrome and Calcium Metabolism
B. A. Lamberg and others ....p. 317
Conn's Syndrome: Effect of Amphenone
J. J. Hoet Jr. and L. Molineaux ....p. 375
Three Types of Long-Acting Corticotrophin Preparations
J. Van der Vies ....p. 401

Conn's Syndrome: Effect of Amphenone.—The authors describe a case of primary aldosteronism in a 54-year-old farmer who was admitted to hospital. The patient had hypertension, hypopotassemia, and hypochloremic alkalosis with urinary sodium and potassium loss. The inhibition of aldosterone secretion by the administration of amphenone, or amphenone B, which is 3,3-bis [p-aminophenyl]-2-butanone dihydrochloride, and the associated changes in the urinary and blood electrolytes made it possible to focus attention on the mineralocorticoid secretion of the adrenal gland in this patient, since it induced a restoration to normal of the abnormal biochemical blood picture. The patient died suddenly of a cerebrovascular accident. At autopsy a left adrenal adenoma, weighing 13 Gm. and mainly containing cells resembling those of the glomerular zone, was found. The test with amphenone in this patient was an important step in differentiating the role of adrenal factors from a purely renal abnormality. The biochemical response to an adrenal inhibitor might thus prove to be of great value in elucidating the role of the adrenocortical hormone secretion in cases of renal potassium wastage.

Am. Journal Obstetrics & Gynecology, St. Louis

79:833-1040 (May) 1960. Partial Index

A Pressor Substance (Hysterotonin) Occurring in Toxemia
C. A. Hunter Jr. and W. F. Howard ....p. 838
ABO(H) Blood Incompatibility as a Cause of Infertility
S. J. Behrman and others ....p. 847
Management of Gynecologic-Urologic Complications
J. W. Kelso and J. W. Funnell ....p. 856
The Saginaw Study of *Perinatal Mortality*
I. Berry Jr. and C. E. Toshach ....p. 871
Perinatal Mortality Surveys
A. G. King ....p. 876
Parenteral Iron Therapy in Anemia of Pregnancy
F. B. Hapke, J. L. Stauf and J. C. Ullery ....p. 886

A Pressor Substance Ocurring in Toxemia.—The authors used muscle strips of rabbit aorta as a test organ for assay of amniotic fluid and decidual and placental extracts obtained during the last 3 months of pregnancy and during labor from patients with acute toxemia. Isolated uterine muscle strips obtained from virgin guinea pigs and a pithed nephrectomized cat were employed for studying the vasopressor effects of the amniotic fluid and placental and decidual extracts. The antidiuretic effect of the decidual extracts was tested on male rats. The results of these tests revealed for the first time the presence of a pressor substance in patients with toxemia of pregnancy. For this substance the authors have suggested the term "hysterotonin." This pressor substance was found in highest concentration in the decidua and in amniotic fluid. Hysterotonin seems to be a polypeptide formed by an enzymatic reaction, differing from any previously described polypeptide. No antidiuretic action can be ascribed to this pressor substance.

ABO(H) Blood Incompatibility as *Cause of Infertility*.—The authors present a possible causative factor for unexplained infertility in anatomically and physiologically healthy couples, based on incompatibility of the ABO(H) blood system wherein the antigens carried by the spermatozoa are blocked or immobilized by the antibodies present in the cervical secretion. Of 102 such infertile couples who had consulted the gynecology clinic and department of urology at the University of Michigan Medical Center in Ann Arbor, Michigan, 89 (87.3%) were found to have incompatible matings as compared with 66 (38.6%) among 171 fertile couples or the American population at large. This is considered to be statistically significant. In 7 additional couples originally labeled as infertile with incompatible matings, the wives conceived after 10 years of infertility and all the offspring were of type O. This lends support to the general hypothesis, as it would indicate that the A or B fathers were heterozygous and the children were born of homospecific pregnancies. There were 58 (57%)nonsecretors among the infertile group as compared with 46 (27%) in the fertile group, and 21 (38.8%) aberrant secretors among the infertile group as compared with 2 (1%) in the fertile group. Despite the considerable increase in nonsecretors among the infertile group, it is, according to the present knowledge, totally unrelated to the ABO blood system and its significance at this time remains obscure.

American Journal Clinical Nutrition, New York

8:131-258 (March-April) 1960. Partial Index

Intestinal Absorption of Sugars and Amino Acids
J. H. Quastel ....p. 137
Malabsorption Syndrome: Pathogenesis
W. T. Cooke ....p. 167
Malabsorption Syndrome: Clinical and Pathologic Aspects
D. Adlersberg ....p. 173
Hematologic Aspects of Sprue
F. H. Gardner ....p. 179
Management of Primary Intestinal Malabsorption
A. B. French, H. M. Pollard, and others ....p. 187
Composition of Dietary Fat and Adipose Tissue
D. M. Hegsted, C. Whyman, and others ....p. 209

Composition of Dietary Fat and Adipose Tissue.—The authors analyzed the abdominal fat of hens fed diets containing different fats. They were surprised to find how accurately the fatty acid composition of the adipose tissue reflected the composition of the fat included in the diet. The hens consuming coconut oil had the highest serum cholesterol values. The amount of vascular sudanophilia was least in the group receiving safflower oil. Although it would appear that the kind of dietary fat influenced the serum cholesterol levels and the development of vascular sudanophilia, differences in production of eggs in this experiment limit the conclusions that can be drawn. If the findings in hens are applicable to man, they suggest a method for estimating the dietary habits with regard to fat, and may be of interest in view of the extensive studies now underway in all parts of the world upon the nutritional role of fats of different composition, in coronary heart disease and atherosclerosis.

American Surgeon, Baltimore

26:189-312 (April) 1960. Partial Index

Perfusion of Coronary Sinus with Gaseous Oxygen
J. L. Talbert and others ....p. 189
Hypertrophic Pyloric Stenosis in Adults
E. S. Stafford ....p. 193
Two Unusual Urethroplasties
W. W. Scott ....p. 196
Anatomical Variations in Congenital Aortic Stenosis
F. C. Spencer and others ....p. 204
Coronary Endarterectomy
D. C. Sabiston Jr. ....p. 217
Open Heart Surgery During Cardiopulmonary Bypass
H. T. Bahnson and others ....p. 227

Replacement of Vertebral Bodies by Bone Grafts
D. Boling and others ....p. 236
Iatrogenic Intraperitoneal Dissemination of a Fibrosarcoma
J. R. Cantrell and L. H. Riley Jr. ....p. 248

Replacement of Vertebral Bodies by Bone Grafts.—Six cases have been reported with photographs of relevant roentgenograms demonstrating destruction or extensive damage of cervical and lumbar vertebrae by infection, tumor, or trauma. These cases illustrate the feasibility of direct surgical attack upon the diseased area with replacement of the diseased vertebral bodies by bone grafts. Collapse of the vertebral column was thus prevented, and more rapid and safe mobilization of the patients was achieved. Demonstrated, too, is the advantage of direct biopsy to give accurate diagnosis in destructive lesions of the vertebral bodies.

Iatrogenic Dissemination of Fibrosarcoma.—A 37-year-old man was hospitalized because of abdominal pain. He had undergone laparotomy 1 year previously for peptic ulcer with pyloric obstruction. A lemon-like mass (fibrosarcoma), found in the left upper quadrant of the abdominal wall, was removed. On a 2nd admission of the patient to the hospital, tender nodules were detected, laterally to a healed left rectum scar. A 2nd operation was performed. A tumor had grown beneath the externally palpable masses, through the posterior rectal sheath and parietal peritoneum, and into the omentum which was adherent to the old incision. Tumor implants were scattered over the serosal surfaces of the peritoneal cavity. A palliative resection of the abdominal wall recurrence was carried out, and there was an uneventful postoperative period. Six months later the patient again complained of abdominal pain; a 5 by 5 cm. mass was found below the umbilicus and several nodules below the tantalum mesh which had been used to close the surgical wound. The patient died within 4 months after the 2nd recurrence. Dissemination of neoplastic cells may develop from a local wound, intestinal suture-line, graft-donor-site implantation, or from blood stream dissemination. In order to prevent iatrogenic dissemination, all tumors arising in the abdominal wall should be treated with the care required for any malignant neoplasm.

Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

83:615-794 (April) 1960. Partial Index

Roentgenologic Manifestations of Fracture of Orbital Floor
J. R. Lewin, D. H. Rhodes Jr., and E. J. Pavsek ....p. 628
Classification of Cervical Spine Injuries
H. F. Forsyth ....p. 633
Unilateral Thoracic Spondylosis
R. Shapiro and H. D. Batt ....p. 660
Little Leaguer's Elbow
B. G. Brogdon and N. E. Crow ....p. 671
Roentgen Manifestations of Synovial Osteochondromatosis
C. Zimmerman and V. Sayegh ....p. 680
Polyostotic Bone Sarcoma Associated with Osteitis Deformans
W. J. Esposito and A. S. Berne ....p. 698
Skeletal Metastases from Malignant Testicular Tumors
P. W. Sum, B. Roswit, and S. M. Unger ....p. 704
Bone Metastasis in Gastrointestinal and Bronchial Carcinoids
F. B. Toomey and B. Felson ....p. 709
The Skull in Hyperparathyroid Bone Disease
K. Ellis and R. J. Hochstim ....p. 732
Roentgen Aspects of Tietze's Syndrome
A. B. Skorneck ....p. 748

Roentgen Aspects of Tietze's Syndrome.—The author presents histories of 2 patients who had painful hypertrophy of costal cartilages and bone. This condition, known as Tietze's syndrome, is a benign self-limited condition of unknown origin, but it must be differentiated from more serious causes of chest pain. Since roentgenographic examination of the chest is now performed in any patient with chest pain, the roentgenologic findings are important in the differentiation. They consist of hypertrophy of the costal cartilages, best demonstrated in tangential views, and excess calcification of these cartilages. There may also be periosteal reaction with increased size and density of the affected ribs. The second ribs are the most commonly affected. The condition seems to be an unusual osteochondritis of undetermined cause.

Anesthesiology, Philadelphia

21:135-236 (March-April) 1960. Partial Index

Hyperventilation with Oxygen: Cause of Cerebral Hypoxia
K. Sugioka and D. A. Davis p. 135
Dual Neuromuscular Block in Man
H. C. Churchill-Davidson and others p. 144
Effects of Barbiturates on Skeletal Muscle Function
R. L. Borgman and others p. 150
Endotracheal Intubation: Effects on Blood Pressure and Pulse
C. C. Wycoff p. 153
Circulatory Changes Due to Pneumothorax in Surgical Patients
T. H. Li, F. Rheinlander, and B. Esten p. 171
Monitoring Muscular Relaxation by Abdominal Electromyogram
B. R. Fink p. 178
The Electrocardiogram During Anesthesia and Surgery
T. H. Cannard and others p. 194

Hyperventilation with Oxygen and Cerebral Hypoxia.—A demonstration by other investigators that active or passive hyperventilation resulted in decreased cerebral blood flow suggested to the authors the possibility that this decreased blood flow might result in cerebral hypoxia even in the presence of increased arterial oxygen saturation. To explore this problem the authors resorted to the use of the oxygen electrode in studies on dogs. They performed quantitative measurements of cerebral oxygen pressure in anesthetized dogs during spontaneous respiration and during hyperventilation. The results were as follows: (1) a 90% rise in cerebral oxygen pressure with the inspiration of pure oxygen by the spontaneously breathing dog; (2) a marked drop in cerebral oxygen tension from a normal of 8 to 15 mm. to 5 mm. Hg as a result of hyperventilation, whether with room air or with 100% oxygen; (3) a close correlation between low alveolar carbon dioxide content and a low cerebral oxygen pressure; (4) a dramatic rise in cerebral oxygen tension when carbon dioxide is added to the inspired gases during hyperventilation and the prompt fall to a low level when carbon dioxide is removed. The conclusion is drawn that cerebral hypoxia may be caused by hyperventilation in the dog and that if this is true in human subjects, perhaps the use of hyperventilation in anesthesia and resuscitation may be harmful.

Angiology, Baltimore

11:99-150 (April) 1960. Partial Index

Aortic Valve Transplants
G. Murray p. 99
Carotid-Basilar Artery Anastomosis and Tic Douloureux
I. J. Jackson and R. Garza-Mercado p. 103
Blood Flow in Postsympathetomy Patients
V. A. Gilbertsen, E. J. Emerson, and F. J. Kottke p. 139

Carotid-Basilar Artery Anastomosis and Tic Douloureux.—The authors present the history of a 33-year-old woman who reported that 4 weeks before admission she was awakened by a sharp pain over the vertex and later there was hypesthesia and a feeling of weakness in her left arm. Afterwards she experienced a dull pain in the distribution of the left trigeminal nerve. Five and 8 months earlier, the woman had had attacks of tic douloureux on the left side lasting from 1 to 3 weeks. A bilateral percutaneous arteriogram was made and serial roentgenograms were taken at 1-second intervals. A vessel was visualized coming off the posterior aspect of the carotid syphon at the level of the sella turcica and going posteriorly and inferiorly, joining the basilar artery at the junction of its upper and middle third. The upper third of the basilar artery was filled with contrast material from the anastomotic vessel.

This anomaly is known as the carotid-basilar anastomosis. The trigeminal artery is a branch of the carotid in the embryo and tends to disappear. When it persists in the adult as an anomalous branch its course, posteriorly, is adjacent to the trigeminal nerve. Because of this relationship to the trigeminal nerve, it has been suggested that this anomalous trigeminal artery could cause tic douloureux. There have been reports of only 32 cases of persistent carotid basilar anastomosis, of which 15 were detected before 1950 as incidental autopsy findings. Since 1950, 17 patients have had this anomaly diagnosed antemortem by means of arteriography. None of the previously reported patients had tic douloureux.

Ann. Otol. Rhin. & Laryng., St. Louis

69:1-308 (March) 1960. Partial Index

Epithelial Neoplasms of Larynx
J. A. Maher p. 73
Myoblastoma of Larynx
S. F. Balshi p. 115
Variables Involved in Automatic Audiometry
A. Epstein p. 137
Tracheotomy in Head and Chest Injuries
B. D. Bryan p. 165
The Temporal Bone in Paget's Disease
L. E. Griffey p. 178
Laryngectomy: Past, Present, and Future
N. Jesberg p. 181
Results of 999 Stapes Mobilization Operations
C. M. Kos, J. L. Shapley, and P. B. Iles p. 206
Some Unsolved Problems of Stapes Mobilization
D. K. Lewis p. 222
Psychological Considerations in Management of Cancer
D. Miller p. 236
Osteoma of the Frontal Sinus
W. W. Montgomery p. 245

Tracheotomy in Head and Chest Injuries.—In head and chest injuries tracheotomy may be the only means of preventing a fatal outcome. Traumatic wet lung may result when the body is thrown against steering wheel or dash board. If this injury is not fatal at once, the clinical signs may be slight. If the increasing wetness of the lung is not relieved, more and more alveoli become blocked, and the patient may succumb to asphyxia. Blocking of the alveoli produces changes in blood chemistry such as anoxemia, acidosis, increase in serum potassium, and low sodium and chloride levels. These in turn produce central nervous system damage that may cause death. Improved exchange of oxygen and carbon dioxide in the lungs is imperative.

Tracheotomy is helpful in patients with severe head and chest injuries for the following reasons: (1) It reduces resistance to the flow of air into and out of the trachea by by-passing the narrow glottic chink and eliminating the resistance and turbulence of the pharynx. (2) It preserves the cough reflex while eliminating the bechic blast. The tussive squeeze is still intact. It is this tussive squeeze that pushes secretions into the larger bronchi where they may be reached with a catheter passed through the tracheotomy tube. (3) Tracheotomy requires no help from the patient. The airways may be kept free from secretions without any unusual technical skill. (4) Tracheotomy helps drain mediastinal emphysema of hemorrhage since the tracheotomy opening is connected with fascial planes which extend into the mediastinum. (5) It reduces the dead air space. After tracheotomy 2000 cc. of air or oxygen is given per minute. This may be life-saving in a patient with severly injured lung or brain tissue. Tracheotomy should be done early. Too frequently it is performed too late.

British Medical Journal, London

1:893-984 (March 26) 1960. Partial Index

Dermatology in a General Hospital
H. R. Vickers ....p. 893
The Brain and Mental Retardation
L. Crome ....p. 897
Transient Amino-aciduria in Potassium Depletion
L. A. Davidson, C. T. Flear, and K. W. Donald ....p. 911
Prophylaxis with Oral Penicillin in Rheumatic Fever
S. Cope and others ....p. 913
Tumours of the Hand
H. G. Stack ....p. 919
Physical Activity After Acute Cardiac Infarction
K. A. J. Jarvinen ....p. 922
Liver-function in Infectious Mononucleosis
S. B. Rosalki ....p. 929

Liver-Function in Infectious Mononucleosis.—Serum glutamic-oxalacetic transaminase (SGO-T), glutamic-pyruvic transaminase (SGP-T), and liver function studies were carried out on 23 patients with infectious mononucleosis during a period of 12 months. All patients had fever, sore throat, and lymph-node enlargement affecting the posterior cervical and, sometimes, the axillary and inguinal nodes. Raised transaminase values were observed in 18 of 19 seropositive cases and in 2 of 4 seronegative cases. The levels of activity of both enzymes were increased during the 1st week of illness, were maximal during the 2nd week, and returned to normal about 5 weeks from its commencement. The SGO-T and SGP-T levels ran roughly parallel, the SGP-T level exceeding that of the SGO-T in about two-thirds of the cases. Transaminase values were below 500 units per milliliter in all but 2 patients; high levels were not necessarily associated with severe illness. Variations in the individual patient's clinical state were reflected in alterations of the transaminase levels. Conventional liver-function tests were less often abnormal and were not affected so early. Zinc sulphate turbidity and serum γ-globulin level were sometimes raised some months after recovery, when other tests were normal; this was thought to be related to persisting antibodies. Findings confirm that liver involvement is a usual feature of the disease. It has been suggested that patients with infectious mononucleosis should be treated with a regime of high-carbohydrate, high-protein, and low-fat diet, vitamin supplements, parenterally given fluids if there is anorexia, and protracted rest.

Archivum Chirurgicum Neerlandicum, Arnhem

12:1-100 (no. 1) 1960. Partial Index

The Anatomy of Recurrent Hernia
W. van der Slikke and F. A. Koopmans ....p. 13
Treatment of Oesophageal Varices
P. J. Klopper ....p. 48
Prostatectomy According to Millin and to Hryntschak
W. A. Moonen and S. G. Rinsma ....p. 63
Hydrocephalus Internus
W. Luyendijk and J. A. Noordijk ....p. 87

Treatment of Esophageal Varices.—In the Surgical Clinic of the University of Amsterdam acute massive bleeding from esophageal varices, not responding to the balloon tamponade of Sengstaken-Blakemore, is treated by ligation of the esophageal varices according to the method of Boerema-Crile. This measure controls the bleeding but does not complete the treatment. Partial esophago-gastrectomy has been used as the definitive method, and it was usually carried out in 2 stages; splenectomy was the first-stage operation and it generally counteracted hypersplenism. About 14 days after the splenectomy, the partial esophago-gastrectomy was performed. This therapy in 2 stages reduces the diffuse bleeding as a result of thrombocytopenia and with it the death rate. Continuity is restored by Boerema's method of resection and formation of a tubular stomach. A large part of the gastric fundus is removed. The thoracic esophagus is obliquely transected at the height of the hilus of the lung. The tube-shaped stomach is then placed in the posterior mediastinum and the excessive length is removed. The anastomosis between the esophagus and the newly-formed stomach is made by the end-to-end technique. There were 6 postoperative deaths in a series of 27 patients who underwent partial esophago-gastrectomy. Eleven had extrahepatic portal hypertension, and in 16 the lesion was intrahepatic. Of those with extrahepatic block, 7 were less than 10 years old and the others were less than 20. Most of the patients with intrahepatic lesions were over 40 years old. One of the advantages of the partial esophago-gastrectomy is the fact that the portal circulation remains normal, in contrast to what happens in the shunt procedures, and this may explain the small number of hepatic failures seen in this series.

Annals of Surgery, Philadelphia

151:441-620 (April) 1960. Partial Index

Influence of Blood Sugar Levels Upon Renal Blood Flow
G. Bounous and H. B. Shumacker Jr. ....p. 441
Pulmonary Abscess in Infancy and Childhood
T. C. Moore and J. S. Battersby ....p. 496
Role of Pylorus in Prevention of "Dumping Syndrome"
S. R. Friesen and E. Rieger ....p. 517
Pancreatic Calcification and Cancer of Pancreas
A. Paulino-Netto and others ....p. 530
Repair of Tendon Injuries of the Hand
R. E. S. Young and J. M. Harmon ....p. 562
Pelvic Exenteration Operations
A. Brunschwig and W. Daniel ....p. 571
Dupuytren's Contracture
A. Stein and others ....p. 577

Pancreatic Calcification and Cancer of Pancreas.—The authors report on 417 patients with carcinoma of the pancreas and 100 patients with chronic pancreatitis. Of these patients, 6 (1.4%) had pancreatic calcifications, and 24 of the 100 patients with chronic pancreatitis had pancreatic calcinosis as revealed by roentgenographic examination, surgical intervention, or autopsy. Alcohol probably was the causative agent in 33 of the 100 patients with chronic pancreatitis. Seventeen (70.8%) of the 24 patients with pancreatic lithiasis were alcoholics. Although pancreatic calcifications were rare among the patients with carcinoma of the pancreas, pancreatic carcinoma was not uncommon in the patients with chronic pancreatitis, in 6 of whom the diagnosis of cancer of the pancreas was confirmed by exploratory laparotomy. These 6 patients were in the group of 24 patients with pancreatic calcifications, an incidence of 25%. Not 1 patient without calcifications, among the 100 patients with chronic pancreatitis, had carcinoma of the pancreas. The incidence of cancer of the pancreas in patients with pancreatic calcificatinos is high enough to suggest a casual or precursory relationship between the 2 conditions, based on the concept of chronic irritation. Careful evaluation of all patients with pancreatic calcification should be made with a thought to removal of the entire pancreas if any *possibility* of carcinoma exists.

Pelvic Exenteration Operations.—Of 592 women who underwent pelvic exenteration operations, 457 were operated on for cancer of the cervix, and 135 were operated on for other forms of malignant neoplasms in the uterus or in adjacent sites. One hundred two of the 592 patients died within 30 days after the operation, a mortality of 17.2%; 35 patients died after 30 days, a total mortality of 137 patients (23%). Of the 592 patients, 388 were operated on between September 1947 and Dec. 31, 1954; of these, 66 survived from 5 to 12 years, a survival rate of 17%. Of those who survived at least 5 years, 12 died up to 9 years and 7 months after the operation. Only 1 of the 12 died of distant metastases from the original tumor. One died of metastases from a 2nd primary tumor in another organ system (hypernephroma). Three are living over 5 years, with recurrences; one is clinically well after 7 years; 2 are deteriorating because of active metastases. Of the 52 patients who are now surviving and free from cancer, 1 has survived for 12 years, 4 for 11 years, 3 for 10 years, 5 for 9 years, 6 for 8 years, 10 for 7 years, 10 for 6 years, and 13 for 5 years. The fact *that this long salvage is sufficiently repetitive (66 times)* in one hospital service indicates that such extended surgical attack on certain forms of advanced cancer can effect long-range control of cancers regarded as hopeless and beyond local standard surgical interventions or irradiation therapy.

Australasian Annals of Medicine, Sydney

9:1-80 (no. 1) 1960. Partial Index

Primary Pulmonary Hypertension
H. Fleming ....p. 18
Clinico-Pathological Features of Leucoencephalitis
G. K. Vanderfield and others ....p. 29
Treatment of Severe Diabetic Ketosis
B. Hudson, M. Bick, and F. I. R. Martin ....p. 34
Humoral Factors in Liver Regeneration
P. E. Hughes ....p. 41
Unilateral Multicystic Kidney in Childhood
D. Bialestock ....p. 44
Use of an Aldosterone Antagonist in Cirrhosis
M. R. Playoust and C. R. B. Blackburn ....p. 64

Primary Pulmonary Hypertension.—Eight cases of primary or idiopathic pulmonary hypertension were seen in the course of 1 year among 500 cases of cardiac, or suspected cardiac, disease. Six of the 8 patients were young women. A high incidence in young women has been noted by others. The presenting symptom in 6 patients was dyspnea on exertion. In several patients the dyspnea was accompanied by lassitude, weakness, and syncope. Syncope is due to the low cardiac output with acute right ventricular failure. Constant dizziness is common terminally. Angina pectoris is of classical type and is due to functional coronary ischemia secondary to severely restricted cardiac output. Sensitivity to cold is frequent. Cyanosis is largely peripheral, but in advanced stages it may extend centrally, and the trunk may show a sinister blue, marble-like mottling. The jugular venous pressure is always raised. Study of the jugular venous pulse would avoid many errors and delays in diagnosis. Cardiac catheterization will confirm the diagnosis and assess the pulmonary vascular resistance. On palpation of the chest, hyperdynamic pulsation of the right ventricle and pulmonary artery, and palpable closure of the pulmonary valve, are characteristic. Polycythemia and arterial desaturation are common. Since the etiology of the condition is unknown, causal treatment is impossible. The disease progresses at a variable rate, leading to death from right heart failure or from sudden arrhythmia.

British Journal of Surgery, Bristol

47:337-456 (Jan.) 1960. Partial Index

Right-Sided or Segmental Ulcerative Colitis
G. Watkinson and others ....p. 337
Primary Malignant Lymphoma of Alimentary Tract
J. G. Azzopardi and T. Menzies ....p. 358
Intestinal Calculi
J. D. Atwell and A. V. Pollock ....p. 367
Pathogenesis of Segmental Enteritis
P. C. Meyer ....p. 375
Secondary Carcinoma of the Penis from Bladder
T. J. Deeley and R. Morrison ....p. 388
Megacolon and Volvulus in Psychotics
I. D. A. Johnston and J. B. Gibson ....p. 394
Wilms's Tumour in the Adult
K. H. Smith ....p. 397
Bladder Papilloma
N. Thompson ....p. 419

Wilms's Tumour in the Adult.—A 23-year-old man complained of lassitude, backache, and loss of weight. He had noticed a lump in the upper abdomen. A large swelling in the right hypochondrium appeared to be a firm, smooth enlargement of the liver. In view of a history of dysentery in Malaya, a provisional diagnosis of amebic abscess of the liver was made, but liver function tests proved to be normal. Laparotomy disclosed a large retroperitoneal tumor that occupied the whole right side of the abdomen and extended into the chest and down to the right iliac fossa, and was adherent to the posterior abdominal wall. A biopsy of the tumor was taken and the abdomen was closed. The histologic findings indicated a malignant tumor of mesenchymal origin, and the cytological aspects suggested embryonic tissue; the presence of 2 primitive tubules were regarded as evidence of nephroblastoma (Wilms's tumor). Under irradiation therapy the condition improved. Later nephrectomy was performed and was followed by irradiation therapy. The patient died 3 months later. Nephroblastoma is rare in adults, being chiefly a neoplasm of childhood. In the literature on nephroblastoma in adults, the author found records of 105 cases, most of them having been reported in the American literature.

Nederlands Tijdschrift v. Geneeskunde, Amsterdam

104:457-500 (March 5) 1960. Partial Index

Administration of Corticosteroids in Tuberculosis
J. K. Kraan ....p. 457
Glasses for Radarscope Reading: Phosphorescent Optotypes
C. K. V. van Dommelen ....p. 464
Hypertrophic Form of Keratosis Follicularis
E. M. Elsback and J. P. Nater ....p. 466

Glasses for Radarscope Reading.—The radarscope is essentially the interior of a cathode-ray tube which has been painted with a phosphorescent substance. Seamen and other persons who have to watch the radar screen and whose eyes require reading glasses should wear their glasses while they watch the radarscope. As the eyepieces, or the radar viewing hoods, are too narrow for most types of spectacle frames, "fit-in glasses" have been designed and have been used with satisfactory results. The author mentions that in persons who have to watch the radar screen or other phosphorescent or fluorescent images the visual acuity *should* be tested for this type of observation. A test card with phosphorescent Snellen optotypes is now available and has been found useful for this type of testing.

WASHINGTON NEWS

Mills Bill Due for Committee Vote . .
Keogh-Simpson Measure . .
Final Action on Health Bills . .

AGED HEALTH CARE BILL: NEXT STEP—COMMITTEE VOTE

The course of the House-passed measure to help the needy elderly meet health costs was slated to be decided shortly after the Senate reconvenes in August after the congressional recess for the Republican and Democratic conventions.

First step will be a vote by the powerful Senate Finance Committee headed by Sen. Harry F. Byrd (D., Va.). The senator said that no more hearings will be held on the legislation, which would set up a voluntary, federal-state program to assist elderly persons who do not have the resources to pay all of their health measures but are otherwise self-sufficient.

Bearing on the congressional outcome of the measure will be the health care planks that the Republicans and Democrats decide to include in their parties' political platforms at the two conventions. There were indications the Democratic party plank would include a call for a compulsory Social Security program to finance some health benefits through higher taxes.

Appearing before the Democratic party's platform committee in Los Angeles, a spokesman for the American Medical Association urged that the party endorse instead the House-approved bill for a federal grant-in-aid program. Dr. Edward R. Annis, of Miami, said Forand-type legislation proposing a Social Security approach was "outright socialization of the financing of medical care."

At two days of hearings before the Senate Finance Committee, the AMA and the Administration backed the principle of the House measure that was developed by chairman Wilbur Mills (D., Ark.) of the House Ways and Means Committee. The AFL-CIO renewed its support of the Forand measure.

Speaking for the insurance industry of the nation, E. J. Faulkner told the committee that giant strides have been made in providing voluntary protection for the whole American people, including the aged.

"Particularly in the short period since 1952 there has been a spectacular growth in group coverage of the aged—especially the retired aged," he noted. "For example, the increasing effectiveness of voluntary programs is demonstrated in a recent survey of private employee benefit programs in New Jersey. Of the 538 plans reporting, 94.9 per cent of today's employees will have hospitalization coverage available to them after retirement. This contrasts with 42.6 per cent in 1950 and 17.5 per cent in 1940."

One of the most prevalent erroneous assumptions in the field of health care for the elderly is that "most of the aged of our country are not able to contribute to financing their own health care costs," said Faulkner. "Where adequate surveys have been made, the inaccuracy of such a presumption is established. For example in Vermont, which has the highest portion of aged citizens of any state, a survey of aged patients showed that over 80 per cent had the resources to pay their doctor bills from Blue Shield or insurance benefits, income or savings."

Many of the proposals before Congress, the witness testified, "would impair or destroy the private practice of medicine, would add immeasurably to our already crushing tax burden, would aggravate our severe public fiscal problems, and would entail other undesirable consequences . . ."

In no event, said Faulkner, should Congress approve any measure going beyond the House program, which rests on a principle of public assistance supported by the insurance.

In other testimony:

- An official of the AFL-CIO backed a modified version of the Forand bill calling for the Social Security approach, but with a $75 deductible and not taking effect until age 68.
- A spokesman for the American Optometric Association proposed that health benefits in the legislation specifically include optometric services.
- The International Chiropractors Association said osteopaths and chiropractors should be on the same footing as physicians as far as the bill is concerned.

KEOGH-SIMPSON BILL TABBED FOR AUGUST ACTION

The House-passed bill to encourage the self-employed to save for their retirement was scheduled for action in the Senate shortly after the lawmakers return from the convention recess in August.

The Keogh-Simpson bill came up for Senate debate shortly before the recess was called in July, but there was not enough time to complete action on it before the Democratic convention started. In reply to a question on the Senate floor, Senate Democratic leader Lyndon B. Johnson of Texas assured the Senate that the measure would definitely be on the agenda when the Senate returned to complete its business for the year.

In an important development, Sen. Harry F. Byrd (D., Va.), chairman of the powerful Senate Finance Committee, threw his wholehearted support to the measure and urged Senate approval. In a speech on the Senate floor, the Senator said the measure as approved by his committee "is the best approach to the problem proposed to date. It will reach individuals in a wide variety of trades and professions in a reasonable manner and within a pattern already existing in the Internal Revenue Code."

The Senate bill contained the basic principle of the House measure authorizing tax deferrals for the self-employed on money set aside in retirement plans, but it includes a number of changes. The most important difference is the requirement in the Senate measure that the self-employed establish retirement plans for their employees in order to qualify for the program.

Senator Byrd noted that the House bill would have resulted in an estimated loss of $365,000,000 a year, while the Senate program would drop revenues by from $150,000,000 to $250,000,000 annually.

Some 20 million self-employed persons such as small businessmen, physicians, dentists, farmers and lawyers would be affected by the legislation, as well as some 10 million of their employees.

Since the Senate bill differs from the House measure, a favorable Senate vote would mean that a House-Senate conference committee would have to either decide upon a compromise or accept the Senate measure. There was little doubt, however, that Senate passage would insure the bill's reaching the White House at this session of Congress. The administration has supported the Senate bill.

Sen. Gordon Allott (R., Colo.) told the Senate as it prepared for the recess that enactment of the measure was long overdue. He said the President, the Treasury Department, and the House "all agreed that the present law does not give self-employed persons tax treatment for their retirement savings comparable with that now accorded the employees covered by the employer-financed pension plans."

"I believe that this legislation . . . will have the overwhelming support of this body," said Senator Allott. "I urge senators on both sides of the aisle to support this measure."

MEDICAL MEASURES TO WHITE HOUSE

Before the five-week recess Congress approved and sent to the White House four bills of interest to the medical profession.

They were:

International Medical Research.—The Senate approved the House version of a bill aimed at spurring international research efforts. The bill authorizes no appropriations and does not create a separate institute of health to manage the program, as the Senate bill had done. Instead, it calls for intensified efforts under existing programs to stimulate cooperation between nations on health research and provides for use of counterpart funds abroad.

Color Additives.—The administration's proposal to allow safe tolerance levels for potentially harmful chemical additives used in foods and cosmetics received final congressional approval. At present, no tolerances are allowed, even though a chemical used in minute quantities could cause no harm. The bill retains the so-called Delaney clause forbidding any tolerance for chemicals found to cause cancer.

Veterans.—The White House received a bill authorizing for the first time outpatient care for veterans with non-service connected disabilities. However, such care could only be provided if the veteran had been authorized admission to a VA hospital or had been treated and discharged from a VA hospital.

Labeling.—Congress cleared legislation endorsed by the American Medical Association that would require manufacturers of household products to place warning labels on products such as cleaners that could be dangerous for children to eat or are highly inflammable.

MISCELLANY

The Federal Trade Commission charged that 10 sellers of contact lenses made false advertising claims that there is no discomfort from wearing the lenses and that they will correct all defects of vision. In all cases, the agency said, the firms claimed that contact lenses can be successfully fitted to anyone's eyes.

The Federal Housing Administration's program of guaranteeing private mortgages for construction of nursing homes was launched with the first application for a 75-bed home proposed for Beckley, W. Va., with a $200,000 mortgage. The mortgage guarantee program, approved by Congress last year, was backed by the American Nursing Home Association, the American Medical Association, and other health groups as a means of encouraging construction of more nursing homes.

Arthur S. Flemming, Secretary of Health, Education, and Welfare, proposed legislation to give the Food and Drug Administration power to inspect all records, files, processes, and facilities of companies manufacturing drugs. The measure would also require drug makers to keep records on clinical experience with new drugs to detect adverse reactions. Flemming conceded there was no chance of congressional action this year due to the lateness of the session.

Dr. Clarence A. Smith was appointed chief of the Public Health Service's Communicable Disease Center in Atlanta, succeeding Dr. Robert J. Anderson, who had been named earlier as Deputy Chief of the Bureau of State Services. Dr. Smith, a graduate of the University of Colorado Medical School, has served his entire professional career in the PHS.

The Senate passed a bill authorizing construction of a 330-bed convalescent hospital in the District of Columbia. The hospital, designed as a model for other institutions, would cost an estimated $4,700,000. Of the 330 beds, 30 would be for completely bedridden patients, 100 for surgical-type rehabilitation cases, and 200 for demonstrative nursing home type care. Two nursing schools would operate at the hospital, designed for non-indigent patients able to afford the $8 to $15 cost per day.

The House was expected to take up before final adjournment legislation to inaugurate a health insurance program with government contributions for already retired federal workers. The House Post Office Committee approved the bill. Aim is to give retired federal employees the same opportunity to participate in a contributory program as is now available for active U. S. workers.

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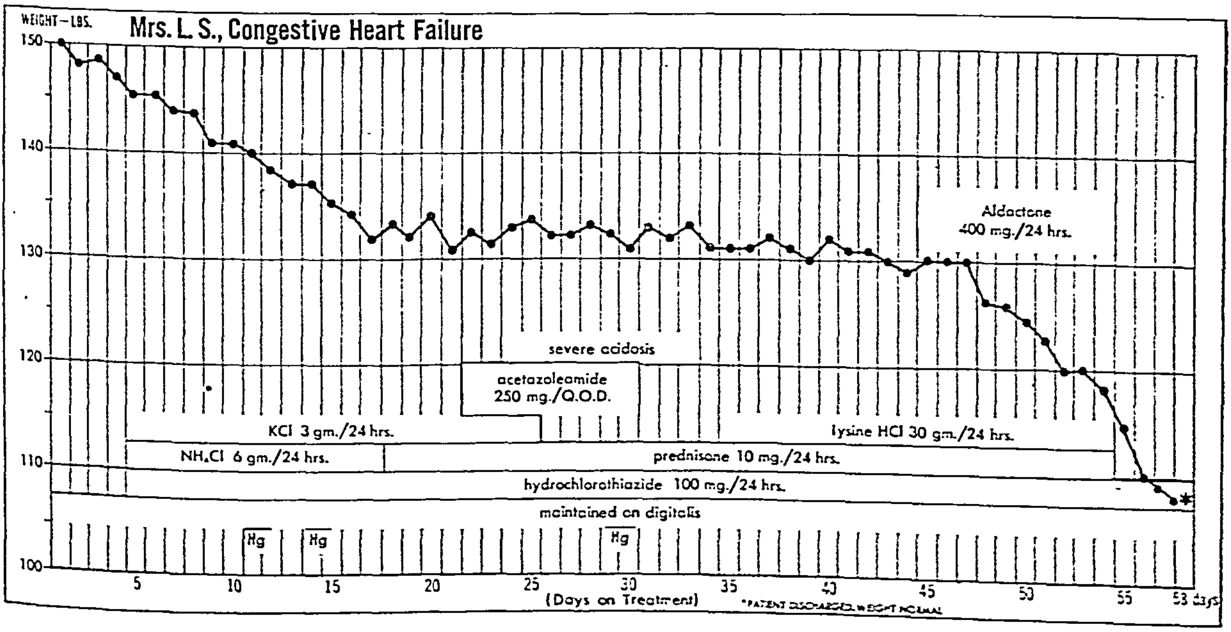

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.

1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 1.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-30.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 26-29.
1963 Annual Meeting, Atlantic City

AMERICAN

1960

July

American Society of Facial Plastic Surgery, Hotel Elysee, New York City, July 22. Dr. Samuel M. Bloom, 123 E. 83d St., New York 28, Secretary.

Postgraduate Medical Assembly of South Texas, The Shamrock Hilton, July 18-20. Mrs. W. H. Dahme, 412 Jesse H. Jones Library Bldg., Texas Medical Center, Houston 25, Executive Secretary.

Rocky Mountain Cancer Conference, Hilton Hotel, Denver, July 20-21. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary, Colorado State Medical Society.

August

American Association of Blood Banks, Jack Tar Hotel, San Francisco, Aug. 21-26. For information write: AABB Central Office, Suite 1619, 30 N. Michigan, Chicago 2.

American Congress of Physical Medicine and Rehabilitation, Mayflower Hotel, Washington, D. C., Aug. 21-26. Mrs. Dorothea C. Augustin, 30 N. Michigan Ave, Chicago 2, Executive Secretary.

American Hospital Association, Civic Auditorium, San Francisco, Aug. 27-Sept. 1. Mr. Maurice J. Norby, 840 N. Lake Shore Dr., Chicago 11, Secretary.

American Institute of Ultrasonics in Medicine, Statler-Hilton Hotel, Washington, D. C., Aug. 20. Dr. Dorothy M. Stillwell, Dept. of Phys. Med. and Rehab., Univ. of Colorado Med. Center, Denver 20, Chairman.

American Physiological Society, Stanford University, Calif., Aug. 22-26. Mr. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

American Society of Clinical Hypnosis, Miami, Fla., Aug. 7-10. Dr. Seymour Hershman, 6770 N. Lincoln Ave., Chicago 46, Secretary.

American Society for Pharmacology and Experimental Therapeutics, University of Washington, Seattle, Aug. 21-25. Dr. Karl H. Beyer, Merck Sharp & Dohme Research Laboratories, West Point, Pa., Secretary.

American Veterinary Medical Association, Denver-Hilton Hotel, Denver, Aug. 15-18. H. E. Kingman Jr., 600 S. Michigan Avenue, Chicago 5, Executive Secretary.

Biological Photographic Association, Inc., Utah Motor Lodge, Salt Lake City, Utah, Aug. 23-26. Miss Jane H. Waters, Box 1668, Grand Central P. O., New York 17, Executive Secretary.

Conference on the Chemical Organization of Cells: Normal and Abnormal, University of Wisconsin, Madison, Aug. 25-27. Dr. J. F. A. McManus, Dept. of Pathology, University of Alabama Medical Center, Birmingham, Chairman.

Gerontological Society, Inc., Mark Hopkins Hotel, San Francisco, Aug. 7-12. Mrs. Marjorie Adler, 660 S. Kingshighway Blvd., St. Louis 10, Administrative Secretary.

National Medical Association, Inc., Penn-Sheraton Hotel, Pittsburgh, Aug. 8-11. Dr. John T. Givens, 1108 Church St., Norfolk, Va., Executive Secretary.

Reno Surgical Society, Mapes Hotel, Reno, Nev, Aug. 18-20. Dr. Gilbert G. Lenz, 505 S. Arlington Ave., Reno, Nevada.

Rocky Mountain Radiological Society, Denver-Hilton Hotel, Denver, Aug. 11-13. Dr. John H. Freed, 4200 E. 9th Ave., Denver 20, Secretary-Treasurer.

St. Joseph's Hospital Annual Clinics, St. Joseph's Hospital, Denver, Aug. 3-5. Dr. W. H. Leitch, St. Joseph's Hospital, 1818 Humboldt St., Denver 18, Chairman.

West Virginia State Medical Association, The Greenbrier, White Sulphur Springs, Aug. 25-27. Mr. Charles Lively, Box 1031, Charleston 24, W. Va., Executive Secretary.

September

American Academy of Pediatrics, and American Academy of General Practice, Louisiana Chapter, Roosevelt Hotel, New Orleans, Sept. 23. Dr. Herbert B. Rothschild, 1520 Louisiana Ave., New Orleans 15, Chairman of Publicity Committee.

American Medical Writers' Association, Hotel Morrison, Chicago, Sept. 30-Oct. 1. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

American Roentgen Ray Society, Ambassador Hotel, Atlantic City, Sept. 27-30. Mr. Hugh Jones, 20 N. Wacker Dr., Chicago 6, Director, Public Relations.

American Society of Clinical Pathologists, Palmer House, Chicago, Sept. 24-Oct. 2. Mr. Claude E. Wells, 445 Lake Shore Drive, Chicago 11, Executive Secretary.

College of American Pathologists, Palmer House, Chicago, Sept. 24-27. Dr. Arthur H. Dearing, 2115 Prudential Plaza, Chicago, Executive Director.

Colorado State Medical Society, Stanley Hotel, Estes Park, Sept. 14-17. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary.

Delaware, Medical Society of, Rehoboth, Del., Sept. Mr. Lawrence C. Morris Jr., 1925 Lovering Ave., Wilmington 6, Del., Executive Secretary.

Flying Physicians Association, third clinical meeting, Western Hills Lodge, Wagoner, Okla., Sept. 6-9. For information write: Flying Physicians Association National Headquarters, P. O. Box 3275, Tulsa, Okla.

Inter-Society Cytology Council, Palmer House, Chicago, Sept. 23-25. Dr. Paul A. Younge, 1101 Beacon St., Brookline 46, Mass., Secretary.

Kentucky State Medical Association, Louisville, Sept. 20-22. Mr. J. P. Sanford, 1169 Eastern Parkway, Louisville 17, Ky., Executive Secretary.

Maryland, Medical and Chirurgical Faculty of the State of, Semiannual Meeting, Ocean City, Sept. 16. Mr. John Sargeant, 1211 Cathedral St., Baltimore 1, Executive Secretary.

Michigan State Medical Society, Detroit, week of Sept. 25. Dr. D. Bruce Wiley, 606 Townsend St., Lansing 15, Mich., Secretary.

Montana Medical Association, Baxter Hotel, Bozeman, Sept. 15-17. Dr. William E. Harris, 114 N. Second, Livingston, Montana, Secretary.

National Cancer Conference, American Cancer Society, Inc., and the National Cancer Institute, Minneapolis, Minnesota, Sept. 13-15. Dr. Roald M. Grant, 521 W. 57th St., New York 19, Coordinator.

National Recreation Congress, Shoreham Hotel, Washington, D. C., Sept. 25-29. Willard B. Stone, 8 W. Eighth St., New York 11, Secretary.

Nevada State Medical Association, Stardust Hotel, Las Vegas, Sept. 7-10. Mr. Nelson B. Neff, P. O. Box 2790, Reno, Nev., Executive Secretary.

New England Society of Anesthesiologists, Bretton Woods, N. H., Sept. 18-19. Dr. Thomas K. Burnap, P. O. Box 81, Kenmore Station P. O., Boston 15.

Oregon State Medical Society, Portland, Sept. 7-9. Mr. Roscoe K. Miller, 2164 S. W. Park Place, Portland 5, Ore., Executive Secretary.

Pacific Dermatologic Association, Empress Hotel, Victoria, British Columbia, Canada, Sept. 1-4. Dr. Edward J. Ringrose, 2636 Telegraph Ave., Berkeley 4, Calif., Secretary-Treasurer.

Society for Pediatric Radiology, Ambassador Hotel, Atlantic City, N. J., Sept. 26. Dr. Richard G. Lester, 412 Union St., S. E., Minneapolis 14, Minn,, Secretary-Treasurer.

Southern Trudeau Society (and Southern Tuberculosis Conference), Hotel Francis Marion, Charleston, S. C., Sept. 14-16. Mr. Judson M. Allred Jr., P. O. Box 9865, Northside Station, Jackson, Miss., Secretary-Treasurer.

Tennessee Valley Medical Assembly, Read House, Chattanooga, Tenn., Sept. 26-27. Dr. Robert A. Waters, 109 Medical Arts Bldg., Chattanooga, Chairman.

Tri-State Medical Assembly, Captain Shreve Hotel, Shreveport, La., Sept. 14-15. Dr. J. W. Wilson Jr., 940 Margaret Place, Shreveport, La., Secretary-Treasurer.

Utah State Medical Association, Hotel Utah Motor Lodge, Salt Lake City, Sept. 20-23. Mr. Harold Bowman, 42 S. 5th East, Salt Lake City 2, Executive Secretary.

Washington State Medical Association, Seattle, Sept. 25-28. Mr. Ralph W. Neill, 1309 Seventh Ave., Seattle 1, Executive Secretary.

Wyoming State Medical Society, Jackson Lake Lodge, Moran, Sept. 7-10. Mr. Arthur R. Abbey, P. O. Box 2036, Cheyenne, Wyo., Executive Secretary.

October

Academy of Psychosomatic Medicine, Benjamin Franklin Hotel, Philadelphia, Oct. 13-15. For information write Dr. Bertram B. Moss, 55 E. Washington, Chicago 2.

American Academy for Cerebral Palsy, Penn-Sheraton Hotel, Pittsburgh, Oct. 5-8. Dr. Joseph D. Russ, 1520 Louisiana Ave., New Orleans 15, Executive Secretary.

American Academy of Ophthalmology & Otolaryngology, Palmer House, Chicago, Oct. 9-14. Dr. William L. Benedict, 15 Second St., S. W., Rochester, Minn., Executive Secretary.

American Academy of Pediatrics, Palmer House, Chicago, Oct. 17-20. Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.

American Association of Medical Clinics, New Orleans, Oct. 6-8. Dr. Joseph B. Davis, 134 N. Washington St., Marion, Ind., Secretary.

American Association of Medical Record Librarians, Olympia Hotel, Seattle, Oct. 10-13. Miss Doris Gleason, 840 N. Lake Shore Dr., Chicago 11, Executive Director.

American Association of Poison Control Centers, Palmer House, Chicago, Oct. 18. Dr. Harry C. Shirkey, 712 S. 30th St., Birmingham, Ala., Chairman, Program Committee.

American Association for the Surgery of Trauma, Coronado Hotel, Coronado, Calif., Oct. 5-7. Dr. William T. Fitts Jr., 3400 Spruce St., Philadelphia 4, Secretary.

American College of Gastroenterology, Bellevue-Stratford Hotel, Philadelphia, Oct. 23-26. Mr. Daniel Weiss, 33 W. 60th St., New York 23, Executive Director.

American College of Surgeons, Clinical Congress, San Francisco, Oct. 10-14. For information write: Dr. William E. Adams, 40 E. Erie St., Chicago 11.

American Fracture Association, El Presidentia Hotel, Mexico, D. F., Mexico, Oct. 30-Nov. 4. Dr. H. W. Wellmerling, 610 Griesheim Bldg., Bloomington,.Ill., Executive Secretary.

American Heart Association, Inc., Jefferson Hotel, St. Louis, Oct. 21-25. Mr. Rome A. Betts, 44 E. 23rd St., New York 10, Exeuctive Director.

American Otorhinologic Society for Plastic Surgery, Inc., Conrad Hilton, Chicago, Oct. 9. Dr. Joseph G. Gilbert, 75 Barberry Lane, Roslyn Heights, L. I., New York, Secretary.

American Public Health Association, San Francisco, Oct. 30-Nov. 4. Dr. Berwyn F. Mattison, 1790 Broadway, New York 19, Executive Director.

American Rhinologic Society, Belmont Hotel, Chicago, Oct. 8. Dr. Robert M. Hansen, 1735 N. Wheeler Ave., Portland 17, Ore., Secretary.

American School Health Association, San Francisco, Oct. 30-Nov. 4. Dr. A. O. DeWeese, 515 E. Main St., Kent, Ohio, Executive Secretary.

American Society of Anesthesiologists, Inc., Statler-Hilton, New York City, Oct. 2-7. Mr. John W. Andes, 515 Busse Hwy., Park Ridge, Ill., Executive Secretary.

(Continued on page 30)

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DEVELOPMENT OF HEAT PYREXIA

Capt. Joseph Gold (MC), U. S. Air Force

In a study of heat stroke, more than 250 observations were made on healthy adult human subjects. Data were obtained on body heat storage, sweat rate, sweat replacement, blood pressure, venous pressure, oxygen consumption, blood gas analyses, hemoconcentration, and osmolarity; and on cardiac output, cardiac shadows, and auscultatory and electrocardiographic findings. During extreme heat exposure there was an increased venous pressure and operational arteriovenous shunt (or its functional equivalent) in the presence of cardiac failure. It is postulated that (1) the primary event in the circulatory collapse of heat pyrexia is high-output cardiac failure, (2) the cessation of sweating is a result of rising venous pressure, (3) older persons are more susceptible because of irreversible circulatory changes, and (4) an effective treatment may be the intravenous administration of saline solution together with rapid digitalization.

THE problem of heat stroke, or heat pyrexia,[1] has been an enigma throughout the ages. Daily and Harrison,[2] in an excellent review clearly defined the three major manifestations of this syndrome which have remained unsolved: 1. Is the mechanism of circulatory collapse peripheral or cardiac? 2. Why do patients stop sweating? 3. What is the most effective means of reducing the pyrexia?

Since much of the work at our laboratory is concerned with the physiological evaluation of subjects undergoing high-heat stresses, it was decided to embark on a program of controlled research studies on the mechanisms which bring about heat stroke. Such a program was feasible because of the rather unique nature of our equipment, as well as the availability of human subjects of all ages. Such equipment includes, for instance, heat chambers capable of duplicating almost any environment (wall temperature, air temperature, air motion, air pressure, and humidity), elaborate telemetering devices, and facilities for cardiovascular analysis. Actually, however, the most important two factors are the availability of healthy, unanesthetized human subjects, and the heat chamber —which can be controlled to bring about impending heat pyrexia in our subjects within one hour.

Because it has been noted countless times that the cardiovascular system apparently takes the brunt of heat exposure,[3] various parameters of this system were investigated. Chief among these was the peripheral venous pressure. Although there are conflicting reports in the literature on what exactly happens to venous pressure,[4] we have noticed at this laboratory that subjects exposed to severely hot environments, such as one of 71.1 C (160 F) at 10 mm. Hg of vapor pressure for one hour, develop peripheral venous distention in the regions of the forehead, face, and neck, even when standing or sitting in an upright position; this distention, moreover, persists for about one half-hour after the subject has been removed from the heat chamber. It was, therefore, suspected that increased venous pressure may play an important role in the pathogenesis of heat stroke, and for this reason it was decided to make a quantitative study of the possible relation between peripheral venous pressure and progressive heat uptake.

Other cues of a cardiovascular nature caused us to pay particular attention to this system in our

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From the Biothermal Section, Biomedical Laboratory, Aerospace Medical Division, Wright Air Development Division, Wright-Patterson Air Force Base.

vapor pressure for 70 minutes. Figure 4 is a consolidation of these data and depicts the change in venous pressure over an extensive range of effective body heat storage. This figure shows that after absorption of 82 effective Calories the venous pressure is increased to over five times its initial rate; at such a high caloric input the subject is just short of heat collapse. Up to this point his face has been ruddy and pink, but during the last five minutes of exposure it has turned almost ashen grey.

Cardiac Output and Blood Gas Analyses.—Subject M was also subjected to cardiac output and blood gas analyses under the environmental conditions of 71.1 C (160 F) and 15 mm. Hg of vapor pressure. Cardiac output was determined by the dye (Evans blue) dilution technique. Oxygen and carbon dioxide content of peripheral venous and arterial blood samples were determined by the Van Slyke procedure; all Van Slyke determinations were carried out in duplicate, and agreement of figures was within an experimental error of ±0.5 vol. %. Figure 5 represents the complete results of these experiments. A level of 10.6 liters per minute was obtained as subject M's resting cardiac output. After he had absorbed about 75 effective Calories, his output was measured at 16.9 liters per minute. Shortly thereafter the premonitory signs of heat stroke set in; the cardiac output was measured once again and determined to be only 6.4 liters per minute. This last determination corresponded in time with a blanching of the subject's superficial vessels and the onset of a dusky grey pallor. At this time, as well as at the beginning, peripheral venous and arterial (brachial artery) blood samples were withdrawn for analysis. These results are indicated in the lower portion of figure 5. It is interesting that the oxygen A-V difference (in the surface circulation of the forearm) at first was 3.9 vol. % but at the end decreased to only 1.6 vol. %. The carbon dioxide A-V difference at first was only 2.4 vol. % but terminally increased to 11.8 vol. %. This wide difference is thought to be due not only to increased carbon dioxide in the venous return, but to a rapid blowing off of carbon dioxide in the lungs, resulting in the low arterial level seen (41.8 vol. %). These studies are partially corroborated in a report by Gwozdz,[11] who found that under environmental temperatures of 50 C (122 F) and 50% relative humidity, subjects exposed for two hours had an increased oxygen content of peripheral venous blood. This was ascribed to a faster rate of blood flow in the cutaneous vessels of the extremities; the circulation rate was found to be increased four-fold.

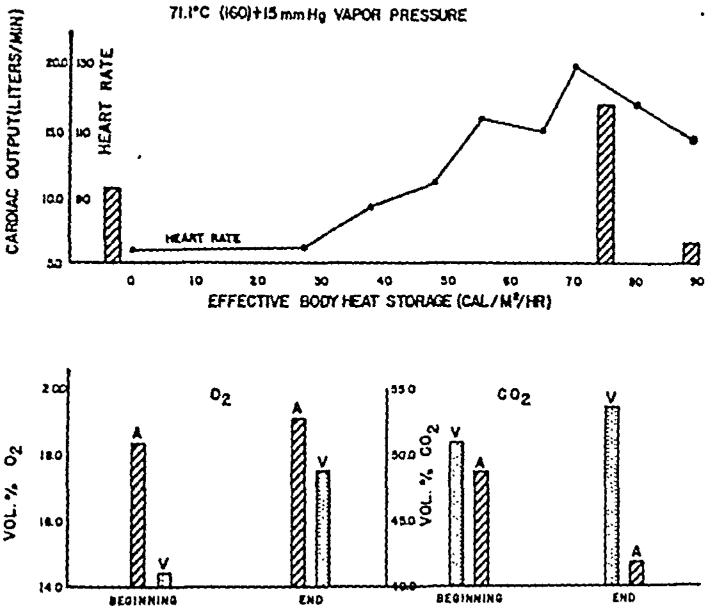

Fig. 5.—*Top*, cardiac output and heart rate as function of increasing effective body heat storage. *Bottom*, changes in oxygen and carbon dioxide content in arterial and peripheral venous blood in instance of severe heat exposure.

Average Sweat Rate.—The average sweat rate in the experiments conducted at 54.4 C (130 F) was about 550 Gm. per hour for two hours, or a total of 1,100 Gm. In the experiments conducted at 71.1 C (160 F) for one hour, the average sweat rate was about 1,000 Gm. These values were determined by nude weights before and after the experiment. The ratio of evaporative rate to total sweat rate in the experiments conducted at 54.4 C was about 0.7; in the studies at 71.1 C it was about 0.55.

Sweat Replacement.—Experiments on sweat replacement were performed as reported in a previous paper.[10] Subjects were fed 1,000 to 1,500 cc. of water of body temperature (37 C) over a period of one to two hours, depending on the experiment. In several instances the added water resulted in a significantly greater output of sweating; in most subjects, however, no change was seen.

Oxygen Consumption.—From a series of 45 unpublished studies performed in this laboratory some time ago, it was shown that oxygen consumption, as measured by the standard BMR technique, increases with increasing heat exposure. A beginning average value of 3.92 cc. O_2 per minute per kilogram of body weight was obtained; this increased to 4.51 cc. per minute after 75 minutes at 71.1 C and 10 mm. Hg of vapor pressure.

Cardiovascular Hemodynamic Studies

Cardiac Shadow Studies.—A series of 35 cardiac shadow studies were performed before and after heat exposure by use of posteroanterior chest plates. Three plates were made of each subject: a control (before) plate; an "exercise" (before) plate which served as a control for an expected decrease in cardiac size due to the tachycardia always seen after heat exposure; and an "after" plate. Cardiac size was determined by measuring the horizontal diameter of the heart. In almost every case a net decrease in heart size was found, even beyond that seen in the control exercise plate. Figure 6 is a sample of the three roentgenograms taken for each study. It shows that the horizontal diameter of the heart is about 1 cm. less (fig. 6*C*) than on the exercise control plate (fig. 6*B*). This decrease in cardiac size is ascribed to an extravascular shift of blood during heat exposure. No changes other than in heart size were seen on any of the plates. It must be stressed, however, that the "after" plate was taken not immediately at, but within five minutes after, the termination of the run. Whether this would have any further bearing on the roentgenographic findings is not known.

Auscultatory Examinations.—Auscultatory examinations made on every subject in the above series (and also in many others) revealed that, after exposure to 54.4 C (130 F) for two hours at 10 mm. Hg of vapor pressure, about 40% developed systolic murmurs heard best over the pulmonic and third left intercostal areas, with fewer focalized in the aortic and apical regions. These murmurs, presumably hemic in origin, ranged from grade 1 to grade 6; several could be heard loudly even with the stethoscope pickup off the chest wall; however, all disappeared within 30 minutes after termination of the heat exposure. A phonocardiogram of the usual systolic murmur heard is presented in figure 7A.

Curiously, on auscultation prior to heat exposure, one of our Mercury astronaut candidates, aged 32 years, presented with a faint intermittent aortic early diastolic murmur. Heat exposure caused this to disappear. His ECG showed a questionable delay in the intrinsic deflection. He was later revaluated cardiovascularly and proven to have a well-compensated aortic insufficiency.

Electrocardiograms.—Electrocardiograms are taken routinely during every heat exposure, but merely for the purpose of monitoring; consequently, only standard limb lead 2 recordings are obtained, but sometimes rectal-forehead leads are used when the subject is in a garment which precludes limb leads. In addition to the usual findings of tachycardia and sinus arrhythmia in young subjects, the two most common abnormalities were flattening and ultimate inversion of the T-wave, and depression of the S-T segment. These were in no way associated with other clinical findings. Various other abnormalities have occurred, however, which are not usually seen. These are nodal rhythm and ectopic beats. In addition, figures 7*B* and *C* are examples of unusual findings. Figure 7*B* is an example of a progressively enlarging T-wave which occurred in cyclic fashion; this was obtained as a sudden change in the normal ECG of a subject who was complaining of a feeling of ill-being at the end of two hours at exposure to a temperature of 54.4 C. The ECG was at first interpreted as a possible transient coronary insufficiency. The subject, however, was sent to the School of Aviation Medicine for five days of extensive evaluation. No cardiovascular abnormalities could be found. Figure 7*C* represents a rectal-forehead lead on a subject who was found to have only occasional premature ventricular extrasystoles. After several hours' exposure to a low level of heat, however, the frequency of the extrasystoles increased markedly, so that they began to occur in pairs; the subject was then removed from the chamber.

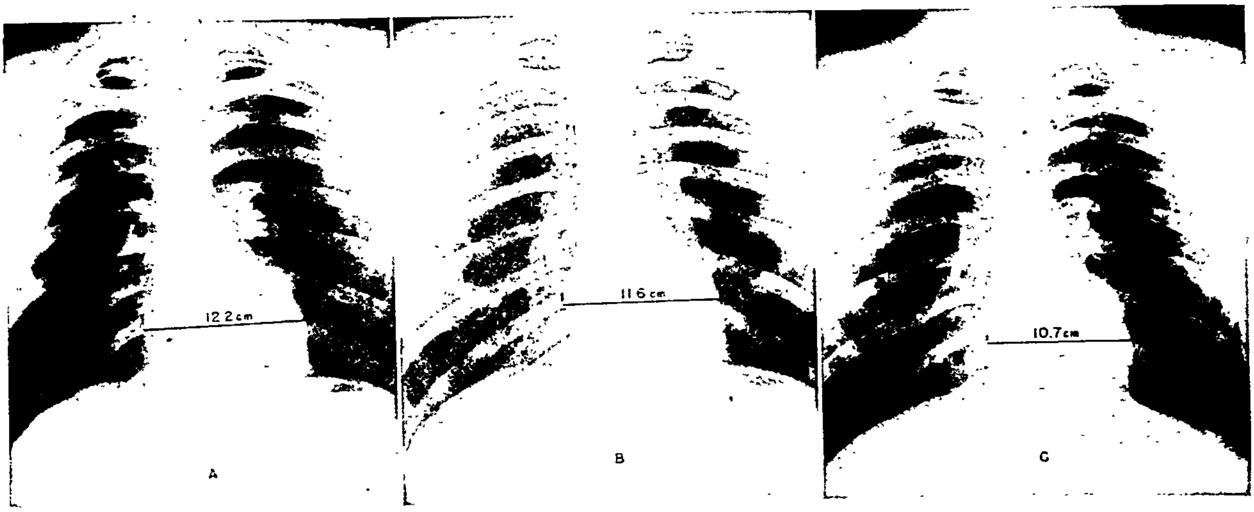

Fig. 6.—Sample of three roentgenograms taken for each of 35 studies. *A*, before "control" plate; heart rate 80. *B*, before "exercise" plate; heart rate 140. *C*, plate taken within five minutes after exposure to 54.4 C and 10 mm. Hg of vapor pressure for two hours; heart rate 136.

Blood Pressure.—Blood pressure readings are also routinely taken (indirectly by sphygmomanometer) on every subject. In younger subjects (below the age of 40 years) a lowering of diastolic pressure is seen practically always; this may go to an extreme in severe exposures, so that it would not be unusual to find a diastolic pressure of zero under these circumstances. This decrease in diastolic pressure (and the resulting increase in pulse pressure) is interpreted as a reflection of decreased peripheral resistance. After the subject's removal from the heat chamber, his diastolic pressure slowly returns to normal.

Older subjects, however, seem to lack this ability to increase pulse pressure by lowering the diastolic component; indeed, if there is any increase at all in pulse pressure, it is usually at the expense of an elevated systolic pressure—an event considered physiologically deleterious.

Increase in pulse pressure via lowering of diastolic pressure, together with increase in heart rate and cardiac output are all regarded as "normal" circulatory compensatory mechanisms in exposure to heat, and as such are peculiar, for the most part, to young subjects (below the age of 40 years). Older subjects do not seem to be too capable of these circulatory adjustments, and it is thought that because of this they are indeed poor subjects for exposure to heat and more susceptible to heat stroke.[12]

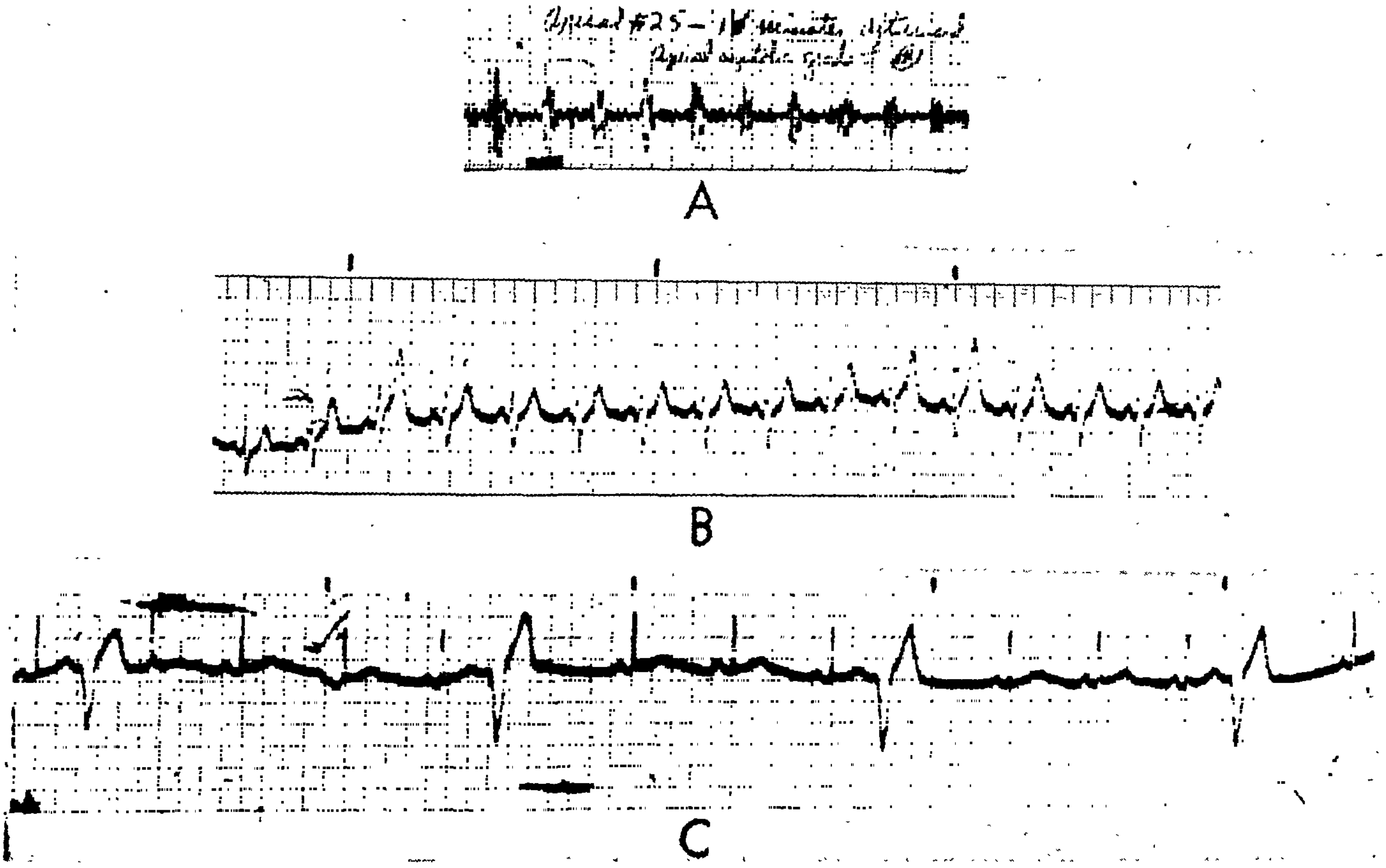

Fig. 7.—*A*, phonocardiogram of apical grade 2 systolic murmur heard 10 minutes after two-hour exposure to 54.4 C and 10 mm. Hg of vapor pressure. *B*, electrocardiogram, standard limb lead 2: progressively enlarging T-wave which occurred in cyclic pattern in one subject after two hours at 54.4 C. Subject at time was complaining of feeling of ill-being. *C*, electrocardiogram, rectal-forehead lead: marked increase in ventricular premature systole after several hours' exposure to low level of heat.

Hemoconcentration.—Hemoconcentration studies were limited to hematocrit readings taken before and after heat exposure at all thermal inputs. Results are in agreement with those of Gibiński, Giec, and Kohat[13] who showed that after two hours at 51 C (123.8 F) (wet bulb 38-41 C [100.4-105.8 F]), the average loss of body weight is 2% and the average hematocrit increased by 2.1%. A few experiments performed in our laboratory, however, showed that the osmotic pressure of plasma (determined by use of a Fisk osmometer) increases slightly during heat exposure.

A Theory of the Development of Heat Pyrexia

Subjective Impressions During Onset of Heat Pyrexia.—After the first half of a "tolerance" exposure (in which a subject is run close to his collapse point) is over, he first becomes conscious of an aura of impending physiological deterioration which has insidiously descended on him. Up to this point he has had a feeling of well-being, despite the intense heat. But now he is definitely aware that his time of heat exposure will be limited. At this point, also, he notices that his ability to concentrate has begun to wane, in that, for example, he cannot concentrate on and read an ordinary magazine article without taking frequent breaks, even though he is interested in its contents. At these breaks, moreover, he becomes increasingly aware of how hot it is. He then returns to his article and is somewhat taken aback to find that he is now looking only at the pictures and turning the pages rapidly, hardly caring what is in them.

As time goes on he notices that his sweat rate has begun to diminish. His face feels dry and hot, and he thinks he can feel a film of dried salt on his cheeks and forehead and especially in the corners of his mouth, which also have begun to feel raw; his hands have become somewhat redder, and they, too, are dry and seem to be getting hotter; and he no longer feels drops of sweat rolling down his trunk under his clothing. Suddenly and abruptly, he feels much worse. He leans forward in his seat in an effort to expose the sweat-soaked clothing on his back more fully to the air, which he hopes will result in a cooling effect due to increased evaporation. It does, but he is somewhat shaken to find that his slightest movement now results in a large increase in heart rate which he can bodily feel. Moreover, he has begun to notice that he is becoming light-headed, especially when he moves his trunk. It is now that the first inkling of the possibility of fainting settles on him; he is certain that he cannot tolerate the heat much longer.

At this point, if he tries to return to the magazine, he will probably throw it to the floor and find himself in a state of utter irritability. He will actually be fully aware of this irritability but will be unable to do anything about it, even should he want to. The goals of the experiment will no longer seem important to him, and he is likely to resent the periodic inflation of the blood pressure cuff on his arm, or being called on to assume a certain position. But he will want to finish the experiment because of high motivation—so as to cause no injury to his self-esteem. Soon he begins to feel the development of paresthesias, particularly in the hands, wrists, feet, ankles, and forelegs. At this point he realizes that he is becoming even more light-headed and that he must terminate the experiment.

Until this time his face has been pinkish-red in color, but abruptly it has turned almost ashen grey. The subject is always removed from the chamber at this point. However, were he not, he would become stuporous, faint, and eventually lapse into the coma of heat stroke. His rectal temperature would be over 104 F (40 C) and skin temperatures would be equally high or higher.

Mechanism of Circulatory Collapse.—Daily and Harrison[2] are of the opinion that the mechanism of circulatory collapse in heat stroke is peripheral, but even they admit that it may be of cardiac origin, especially in older patients who already have heart disease. Moreover, they themselves pose the question why pulmonary edema is encountered clinically if cardiac failure is not the reason for circulatory collapse. Their answers are based on the contention that venous pressure does not rise during heat exposure, as was shown in their experiments with rats.

However, in our experiments with healthy, young, unanesthetized human subjects, it is precisely a rise in venous pressure that is always seen (fig. 3 and 4); moreover, this rise can be quantitatively correlated with effective body heat storage. In addition, if all subjects behave as the stable subject (M) did, it can be seen that cardiac output increases (70% in this case) with increasing body heat storage, and just before the collapse point abruptly decreases (40%) below resting levels. That this pattern of gradual rise and sudden fall in cardiac output may hold true for all subjects, is corroborated by Daily and Harrison's experiments with 10 dogs, in which the cardiac output response coincided almost exactly with subject M's.

The question of A-V shunts now arises. From our data as well as from those of Daily and Harrison,[2] it is evident that during the stage of heat intoxication short of collapse, a massive cutaneous circulation arises which is certainly the functional equivalent of, if not a genuine, A-V shunt. This may well be the cause of the paresthesias commonly felt by subjects (tissue anoxia). Whether or not A-V shunts operate internally for the body as a whole is yet to be determined. Nevertheless, in the face of this enormously increased surface circulation an operational A-V shunt (or its functional equivalent) must be regarded as a route of paramount importance over which a major portion of the circulation passes. (Indeed, is one not justified in assuming that for physiological purposes the body is, figuratively speaking, one huge A-V shunt?)

In summary, cardiac failure, not only accompanied, but preceded, by a rise in venous pressure, together with an operational A-V shunt of substantial magnitude, is evidence not of a peripheral mechanism of circulatory collapse but of a central one. It is therefore postulated that the primary functional pathology in heat stroke which finally brings about circulatory collapse is cardiac failure. The mechanics of this would be as follows: The greatly diminished peripheral resistance allows for an abundantly increased and rapid venous return, which in turn increases the cardiac output. Assuming that the left side of the heart cannot keep pace with the right, this increase in venous return results in an elevation of venous pressure; the sequelae to this rise may be of utmost importance in the pathogenesis of heat stroke, as described below. However, if such a sequence of cardiovascular events holds true, it seems clear that the primary event in circulatory collapse may well be a high output or forward failure of the heart. It is especially under such circumstances that the presence of pulmonary edema can be easily explained. Moreover, it is precisely a high-output type of failure which usually precipitates circulatory collapse before cardiac output drops. For these reasons, then, it is postulated that high-output cardiac failure is the triggering mechanism of circulatory collapse.

Reasons for Cessation of Sweating.—In 1946 Burch[14] demonstrated a marked impairment of sweating in patients with severe congestive heart failure resting in a hot and humid environment. Their rate of water loss was only 27 to 47% of that of normal subjects under similar environmental conditions. However, as their congestive failure subsided, their rate of water loss returned to normal. Severe congestive failure is accompanied by a sizable increase in venous pressure, but as the syndrome subsides, so does the venous pressure. Can it be that the factor which initially causes the diminished sweat rate in congestive failure, is the high venous pressure? And, conversely, when congestive failure subsides, is it the subsiding venous pressure which once again allows the sweating mechanism to function normally?

With many of our own subjects involved in sweat replacement or calorie neutralization studies, in which they were given 1 liter or more of fluid to drink over one hour's time, it has been noticed that toward the end of the experiment, they, too, begin to cease sweating, despite their being given so much extra fluid. However, within 10 minutes after being brought out of the chamber, they once again begin sweating fiercely. This has happened so often as to rule out coincidence. The explanation of this phenomenon may be the same as in Burch's subjects: namely, that at the levels of heat exposure used in this laboratory it is a usual finding that venous pressure increases with increasing body heat storage (fig. 3 and 4). It may therefore be that a gradual cessation of sweating is indeed dependent on this rise of venous pressure. After the subject is removed from the heat chamber, his physiology begins to be restored to normal, and his venous pressure also drops. Again, it may well be that the return of the venous pressure to normal levels releases the sweating mechanism and once again allows it to function freely.

Therefore, from two lines of circumstantial evidence it is postulated that an increasing venous pressure is the trigger mechanism to the cessation of sweating found in victims of heat stroke. As the venous pressure increases, the sweat rate begins to drop off; as venous pressure decreases, the mechanism of sweating is restored.

Relevance of Age As Outstanding Predisposing Factor to Heat Stroke.—Figures 1 and 2 show that during heat stress, subjects of increasing age absorb an increasing amount of effective Calories. This holds true whether they are exposed and given nothing to drink, or whether they are given 1 liter of ice water. The reason for this, as postulated above, is that the circulatory systems of older subjects are already compromised, in that they are no longer capable of undergoing a full range of compensatory adjustments. And, since the circulatory system seems to be the final common pathway [3] for heat dissipation, it is not surprising that older subjects will absorb more from a given thermal exposure; and the more heat is absorbed, the poorer off is the subject. For this reason, then, older subjects are especially predisposed to heat stroke.

Treatment of Heat Pyrexia.—In addition to the classic treatment of this syndrome (rapid body cooling) and on the basis of the experimental evidence and postulates presented in this contribution, it may be advisable to treat the vascular collapse in instances of heat stroke by the simultaneous administration of intravenously given fluids together with a quick-acting cardiac glycoside, the latter being used not only to diminish the risk of pulmonary edema and superimposed cardiac failure but also perhaps to correct for an initial heart failure in the first place.

Summary

Evidence derived from a number of well-controlled experiments shows an increasing venous pressure and operational A-V shunt (or its functional equivalent) in the presence of cardiac failure during extreme heat exposure. It is postulated that the primary event in the circulatory collapse in victims of heat stroke is a high-output type of cardiac failure. In addition, it is postulated that the increase in venous pressure is ultimately responsible for the cessation of sweating seen in this syndrome. Older subjects were found to absorb more heat during a given exposure, and this presumably accounts for their increased susceptibility to heat stroke. Finally, it is proposed that intravenous administration of fluids in combination with simultaneous digitalization may well be an effective treatment for heat stroke, as an adjunct to the classic methods of rapid body cooling.

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INAPPARENT MEASLES AFTER GAMMA GLOBULIN ADMINISTRATION

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The appearance of antibodies and development of immunity to measles was observed in 19 children in whom signs of measles had been prevented, during the course of epidemics, by the administration of gamma globulin. The epidemics occurred in two cottages of an institution for mentally retarded children. Both virus-neutralizing and complement-fixing techniques were used for the serologic tests, and human infant kidney tissue cultures were used for virus isolation. Of 38 susceptible children exposed to measles under these conditions and given gamma globulin, 19 developed measles antibodies without overt signs of the disease. Five of these 19 children failed to contract measles when exposed again seven months later.

In administering gamma globulin to persons who have been exposed to measles, the choice of dose and time of injection are usually based on whether prevention or attenuation is desired. It has been frequently stated[1] that the immunity afforded is only transient if no signs of the disease appear. However, a search of the literature has failed to reveal any substantial data that might support this statement.

The purpose of this paper is to report the development of antibodies and subsequent immunity in 19 children in whom signs of measles had been prevented by the administration of gamma globulin. The observations were made during the course of measles epidemics in an institution for mentally retarded children. The children were kept under close medical supervision, with particular attention to observation for signs of measles after it was recognized in a cottage. Some of the children studied were incapable of describing subjective symptoms but many were reasonably articulate. A number of nonspecific minor illnesses occurred in one of the groups under study, but these were not correlated with the development of measles antibodies. Thus, although mild and nonspecific signs or symptoms may have sometimes accompanied the acquisition of immunity, these 19 subjects did not develop apparent cases of measles.

Materials and Methods

Serologic Tests.—The methods for measles neutralizing and complement-fixing (CF) antibody titrations have been described previously.[2] Briefly, the Edmonston strain of measles and the Hep-2 strain of tissue culture were used for the neutralization test. The challenge dose of virus was between 1,000 and 10,000 infectious units per 0.1 ml., but the end-point of serum titrations was read when a control titration of the test virus showed cytopathic changes at a dilution of 1/100. Equal volumes of virus suspension and twofold serum dilutions were mixed and held for one hour at room temperature. Two-tenths of one milliliter of the mixture was then inoculated into each culture tube. The CF titrations were carried out by the drop method[3] with use of fluids from infected monkey kidney or Hep-2 tissue cultures as antigens. The lowest dilution of serum tested by either method was 1 in 4. For convenience, serums which gave no reaction at this level are recorded as negative, although it must be borne in mind that antibodies may have been present in titers of less than 4.

Virus Isolation Technique.—Blood specimens and throat swabs were tested for measles virus. The throat swabs were extracted with 1 ml. of tissue culture medium and the extracts cleared by centrifugation at 2,000 rpm for 30 minutes. For isolation, 0.1 ml. of whole blood or throat swab extract was inoculated into each of two human infant kidney tissue cultures. One blind passage was made into fresh cultures on the 18th day and kept under observation for a further 21 days.

Gamma Globulin.—The gamma globulin used was obtained from several commercial sources, each lot having a neutralizing titer of 400 per 0.1 ml. as determined in the test outlined above. With the administration of the highest dosage level used (0.1 ml. per pound of body weight) this would not have resulted in passive serum titers above 4, even assuming all the gamma globulin entered the circulation simultaneously.

Measles Epidemics

Cottage 1.—Cottage 1 housed 54 male subjects aged 8 to 27 years. The unit was divided into two semi-independent wings, serviced by the same staff but each containing its own dormitory, dining room, and play area. The subjects in this cottage were all ambulant but had marked mental retardation associated with a variety of syndromes.

The first case of measles occurred in the north wing in a boy who was noted to be ill on March 29, 1959, and developed a rash the next day. Since serum specimens from all the boys in the cottage

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had been tested shortly before this date for measles CF antibodies, it was possible to identify 28 persons with titers of 4 or less. On March 30 each of the 28 was given an intramuscular dose of 0.1 ml. of gamma globulin per pound of body weight. The next case developed 11 days later when on April 10 another boy in the north wing developed measles. His CF titer had been 8 when tested earlier in the year and he had, therefore, received no gamma globulin. A third boy, one who had received gamma globulin, developed modified measles on April 16. No further cases were recognized in the north wing although the staff were expecting more and were watching for signs of illness.

Table 1.—*Measles Antibody Responses in Boys of Cottage 1 Who Had Prior Neutralizing Titers Less Than 4**

No.	Wing	Gamma Globulin March 30	Onset Date of Rush	Pre-epidemic		Post-epidemic	
				CF	Neutralizing	CF	Neutralizing
1	N	—	March 29	0	0	16	360
2	N	—	April 10	8	0	8	180
3	N	+	April 16	0	0	0	64
4	S	—	May 4	4	0	64	180
5	S	+	May 15	0	0	128	180
6	S	+	May 18	0	0	32	32
7	S	+	May 18	0	0	16	45
8	S	+	May 18	0	0	32	45
9	S	+	May 20	0	0	64	22
10	S	+	June 5	0	0	32	45
11	N	+	...	0	0	0	8
12	N	+	...	0	0	...	4
13	N	+	...	0	0	...	6
14	N	+	...	0	0	8	45
15	N	+	...	0	0	8	128
16	S	+	...	0	0	32	45
17	S	+	..	0	0	4	6
18	S	+	...	0	0	16	8
19	S	+	...	0	0	32	16
20	S	+	...	4	0	64	64
21	S	+	...	0	0	0	4
22	S	+	...	0	0	0	±
23	N	+	...	0	0	0	0
24	N	+	...	0	0	0	0
25	N	+	...	0	0	0	0
26	N	+	...	0	0	0	0
27	S	+	...	8	0	0	0

* 0=titer less than 4; ±=delay of challenge virus by serum diluted 1:4.

On May 4, 18 days after the last case in the north wing, the first case occurred in the south wing. This case was also in a boy who had not been given gamma globulin because his CF reaction had been positive though low in titer. Six boys in the south wing who had received gamma globulin developed modified measles during the following month. No further cases were recognized. Temperatures of ill boys in this cottage were not routinely recorded because of the difficulty in handling these patients.

Cottage 2.—Cottage 2 housed about 65 children aged 6 to 13 years. There were some discharges and new admissions during the period of study. This cottage also contained two dormitory rooms, but the children all ate and played together. These subjects represented a higher mental level than those in cottage 1. Most were physically normal and able to describe symptoms. The first case of measles occurred in a child whose rash appeared on July 13, 1958, one day after he had returned from vacation. On July 15, 19 children who had not been in the cottage at the time of the last epidemic three years previously were given 0.05 ml. of gamma globulin per pound of body weight. The children were kept under observation for several weeks, and temperatures of any who appeared ill were recorded. One modified case of measles developed on July 27, 15 days after the first exposure, but no other cases were recognized during the summer.

Measles was accidentally reintroduced into cottage 2 in the winter of 1959 when a child became ill and developed a typical rash on Feb. 2. This patient had contracted the disease outside the cottage during a stay at the institutional hospital. On Feb. 3, 1 ml. of gamma globulin was given to 30 children with histories negative for measles. This dose was used regardless of the child's weight but was equivalent to 0.015 to 0.025 ml. per pound of body weight. Eighteen more cases of measles occurred between Feb. 16 and March 9. Thirteen of these cases were in children who had received the second dose of gamma globulin, and most of these cases were modified in severity.

Serologic Evidence of Measles Infections

Cottage 1.—Blood specimens, drawn from each boy in cottage 1 before the onset of the epidemic, had already been tested for CF antibodies; neutralizing titers were determined later on the same specimens. Thirty-three (51%) had antibodies of both types to a titer of 4 or greater. Four had CF antibodies only, but none had only neutralizing antibodies. In every instance in which the serum was positive by only the CF test, the titer was low. None of the subjects with neutralizing antibodies developed measles and none of them showed any immunologic response on subsequent exposure to the disease. They will not be considered further in this report.

Table 2.—*Neutralizing Antibodies in Selected Group from Cottage 1 from Whom Multiple Specimens Were Obtained*

No.	Wing.	Onset Date of Rash	Mar. 26	Apr. 2	Apr. 7	Apr. 10	May 1	May 25	June 30
3	N	Apr. 16	0	...	0	0	64	...	...
11	N	...	0	0	6	16	6	...	8
12	N	...	0	...	0	0	4	...	...
13	N	...	0	0	0	0	6	...	...
14	N	...	0	...	0	0	45	...	...
15	N	...	0	0	0	...	128	...	...
23	N	...	0	0	0	0	0	...	0
24	N	...	0	0	0	0	0	...	0
25	N	...	0	...	0	...	0	...	0
26	N	...	0	0	0	...	0	...	0
10	S	June 5	0	...	...	...	...	0	45
19	S	...	0	...	...	...	...	0	16
20	S	...	0	...	...	...	...	0	4
27	S	...	0	...	...	...	...	0	0

All persons who developed signs of measles acquired both kinds of measles antibodies during the period of the epidemic (no. 1-10 in table 1). In addition, 11 other boys developed neutralizing antibodies without any recognized signs of disease (no. 11-21). Only five boys remained completely without measles antibodies at the end of the outbreak (no. 23-27). One (no. 22) developed a questionable neutralizing titer.

Insofar as it was possible to determine the dates at which antibodies first appeared in boys with inapparent infections, they coincided with the recognized cases of measles. In the north wing, where overt cases occurred up to April 16, no one developed antibodies after May 1 (table 2). In the south wing, where overt cases occurred up to June 5, two boys developed antibodies without signs of disease between May 25 and June 30 (table 2).

Cottage 2.—Prior to the first outbreak of measles in cottage 2, 9 of the 27 children tested had both CF and neutralizing antibodies, while 15 had neither. Pre-epidemic specimens were not available from either of the cases of measles which were recognized in this outbreak (28 and 29 in table 3), but both patients had moderately high titers after the illness. Five other children from the group of 27 under study (no. 30-34 in table 3) developed measles antibodies during the summer without specific signs of illness.

There was considerable nonspecific febrile illness during the summer in this unit, a situation which is not unusual for such institutions.[4] Three of the five children who developed antibodies without specific signs had rectal temperatures of 100 F (37.8 C) or higher, but so did 15 of 57 children (26%) who showed no change in antibody titer.

When measles was reintroduced into the unit the next winter, none of the children who had developed antibodies previously acquired the disease (table 4). Three of those who had had inapparent infections received gamma globulin again in the winter; they may have been protected thereby, but two (no. 32 and 34) received no further artificial immunization. Three of the original patients with inapparent cases had essentially the same titers after the second epidemic as after the first, while one had an increased titer. Although restimulation of antibodies cannot be ruled out, the similarity of the titers on the different dates suggests that these antibodies were as stable as those acquired in overt disease.

TABLE 3.—*Measles Antibody Responses and History of Minor Illness Without Measles During 1958 Epidemic in Cottage 2**

No.	Gamma Globulin July 15	Onset Date of Measles	Pre-epidemic		Minor Illness	Sept. 17	
			CF	Neutralizing		CF	Neutralizing
28	—	July 13	—	—	...	64	45
29	+	July 24	—	—	...	64	22
30	+	...	0	0	—	32	8
31	+	...	0	0	+	64	22
32	+	...	0	0	+	180	90
33	+	...	0	0	—	...	8
34	+	...	0	0	+	AC	6
36	+	...	0	0	—	AC	0
37	+	...	0	0	+	AC	0
39	—	...	0	0	—	AC	0
40	+	...	0	0	—	AC	0
41	+	...	0	0	—	AC	0
43	—	...	0	0	+	AC	0
44	+	...	0	0	—	0	0
45	+	...	0	0	+	AC	0
46	+	...	0	0	+	0	0

*All children with prior neutralizing titers less than 4. 0=titer less than 4; AC=specimen anticomplementary; titer less than 16.

Again, in the second epidemic as in the first, all subjects who had recognizable measles developed measles antibodies. Three more children acquired antibodies without recognized signs of disease (no. 44-46). Two children with a history of measles four years earlier, but with CF antibodies only, showed an increase in titer without specific illness (no. 47-48). By the end of the second epidemic every child in the group under study possessed measurable measles antibodies.

TABLE 4.—*Measles Antibody Responses and History of Minor Illness During 1959 Epidemic in Cottage 2**

No.	Gamma Globulin Feb. 3	Onset Date of Measles	Pre-epidemic		Minor Illness	March 24	
			CF	Neutralizing		CF	Neutralizing
28	—	7/13/58	64	45	—	32	64
29	—	7/24/58	64	22	—	12	22
30	+	...	32	8	+	4	6
31	+	...	64	22	+	32	22
32	—	...	180	90	—	64	90
33	+	...	...	8	—	...	...
34	—	...	0	6	+	16	45
35	—	2/ 2/59	...	...	...	256	128
36	—	2/16/59	0	0	...	128	64
37	—	3/ 9/59	0	0	...	64	45
38	+	2/16/59	4	0	...	128	64
39	+	2/16/59	0	0	...	180	90
40	+	2/16/59	0	0	...	128	22
41	+	2/19/59	0	0	...	128	360
42	+	2/26/59	0	0	...	128	360
43	+	3/ 5/59	0	0	...	128	45
44	+	...	0	0	+	45	180
45	+	...	0	0	+	128	32
46	+	...	0	0	—	32	128
47	—	2/18/55	4	0	+	96	0
48	—	2/ 8/55	6	0	+	45	45

* All children with neutralizing titers less than 4 prior to 1958 epidemic.

Minor illnesses were prevalent again in February and March, coincident with the measles epidemic. Twenty-seven of 43 children (63%) who showed no change in antibody titer became ill during this period as well as two of the three who acquired antibodies without specific signs of measles.

Relationship Between Titer and Type of Diseases.—Other workers[5] have shown that measles CF and neutralizing antibodies reach peak titers within two weeks of development of the rash and decline slowly during the following months. Thus, provided the time at which specimens are collected is at least two weeks after the onset of rash, and provided that the intervals do not vary grossly, valid comparisons of antibody titers in different persons can be made. In the instances of the children who developed antibodies without illness, the date of onset cannot be determined, but the time of antibody development suggested that infection occurred at about the same time as in overt secondary cases in the same dormitory groups (table 2). The interval between hypothetical onset and collection of the serum specimen has been estimated on this basis, and the titers were compared with those in specimens collected at about the same intervals after overt illnesses. Data on the intervals between illness and date of specimen are given in table 5 and the individual neutralization titers are shown in the figure. Many of the inapparent infections resulted in titers lower than those of any of the apparent cases, and the average titers of the different groups showed marked differences. The antibody titers of the patients with overt cases who received gamma globulin were also lower than those with the unmodified cases, but the number of the latter is too small to allow confidence in the validity of this difference.

Contagiousness of Inapparent Infections

Blood specimens and throat swabs collected from 11 subjects in the north wing of cottage 1 on April 2, 7, and 10 were tested for the presence of measles virus. Two of these persons developed antibodies without illness during this period and four more developed antibodies later in the month, one of them with accompanying overt disease. All virus isolation attempts gave negative results. However, no specimens from patients with unmodified cases of measles were available for parallel testing as positive controls for the efficiency of the method.

Table 5.—*Mean Neutralizing Antibody Titers in Children Experiencing Different Forms of Measles*

	No. Tested	Date of Specimen, Wk. After Onset			Geometric Mean Neutralizing Titer
		Earliest	Latest	Mean	
Unmodified measles	8	2	8	4.8	156
Measles after gamma globulin	11	2	8	5.5	70
Inapparent infections	19	3	11	4.9	22

Epidemiologic data also suggested that children with inapparent infections and possibly modified measles excreted no more than minimal amounts of virus. The index patient in the summer epidemic in cottage 2 developed measles with rash one day after his return to the cottage. Since antibodies appear promptly after the rash,[5b] it was not surprising that no more than six secondary cases ensued. However, five susceptible children (no. 35, 38, 39, 42, and 43) who had not received gamma globulin not only escaped infection from the index case but also were unaffected by exposure to the six subsequent modified or inapparent cases in the cottage during the entire course of their infection. All five children were fully susceptible to infection, as shown by the fact that they developed measles within five weeks of the time when virus was reintroduced the next winter, even though all but one of them (35) had received gamma globulin at this time. The failure of these children to become infected during the summer outbreak suggests that the amount of virus excreted by the children with inapparent infections was small.

In cottage 1, on the other hand, there was some suggestion that inapparent infection may have played a role in maintaining the epidemic. Eighteen days elapsed between the last case in the north wing (a modified case, no. 3 in table 1) and the first case in the south wing (4). While such long intervals have been noted when the second case is modified, it presented an unusually long incubation period for unmodified measles. Four boys developed measles antibodies during this 18-day period, and if any of them served as the actual source of infection for the case in the south wing, two normal intervals of 12 days each would account for the time between the last unmodified case in the north wing (April 10) and the first in the south wing (May 4).

Comment

In 1927, Kingsbury[9a] reported three instances in which a total of 211 children were reexposed to measles four to six months after an initial exposure and administration of immune serum. Only five cases of measles occurred in these children; they had developed no disease at the time of the first exposure, and, furthermore, many cases occurred during the second epidemic in children who had not been present during the earlier one. These epidemics occurred on rubber plantations in Malaya, where medical supervision may have been limited, and perhaps for this reason the observations that were made have been entirely ignored in later studies. Saarelma[9b] reported a reduced attack rate on second exposure in persons who escaped apparent measles when given gamma globulin at the time of initial exposure.

Kingsbury and Saarelma are the only authors to report long-term immunity after prevention of overt measles, but Townsend[7] and Karelitz[8] have both investigated immunity after modified measles. In neither study did any person who had had modified measles report a second bout with the disease during the several years which had elapsed between the original illness and the time of the surveys. All other investigations of immunity after administration of gamma globulin for either modification or prevention of measles seem to have been limited to periods of a few weeks. Several such short-term studies have been made.[9] In most instances, measles was reported in only a small number of reexposed children, and often there was no indication of the total number under study. When such total figures were available, the number of children given gamma globulin who escaped measles after the initial exposure but contracted it later was never more than 50% of the total. The frequently made statement that no immunity is acquired without overt disease is apparently based solely on this insubstantial evidence.

The data presented in the present paper are subject to three possible interpretations. Other workers[9b] have commented on the difficulty of recognizing certain highly modified cases of measles; it is possible that, on closer examination, certain signs of measles could have been recognized in all children who developed antibodies. In view of the evidence that minor illnesses occur frequently in young children,[10] particularly in institutions, it seemed futile to look for mild forms of conjunctivitis, coryza, or cough, and Koplik's spots are often absent in modified cases. The temperature records show no significant correlation with the development of antibodies in the absence of overt measles. If signs of measles did occur in all who developed antibodies they were too mild and nonspecific to serve as an index of infection.

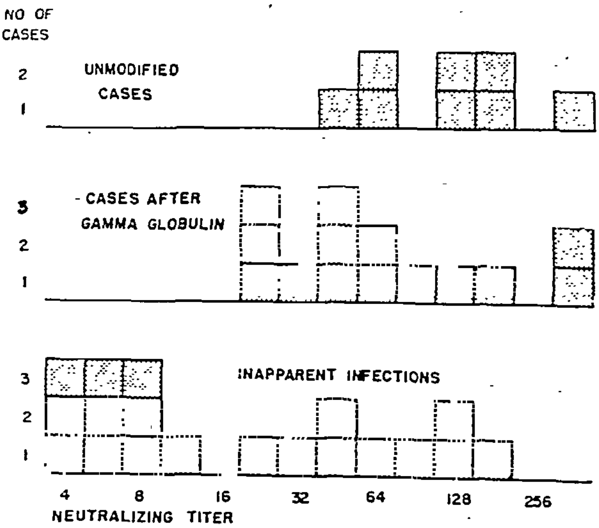
It is conceivable that those who seemed to develop antibodies without measles were persons who were already immune as a result of earlier infection and in whom antibody titers had fallen below the lowest level tested (titer of 4). It has previously been stated that antibody titers do not change either on reexposure or over considerable periods.[11] Two instances were recorded in the present study in which children with a history of measles who had low antibody titers nevertheless developed a considerable increase in titer. These two children remain exceptions to the general finding of antibody stability, and it would seem highly improbable that all the 19 who developed antibodies without disease had had previous unrecorded histories of measles, had lost detectable antibody titers, and had responded with antibody boosts on reexposure. The only interpretation that fits the data for most of those who developed antibodies without recognized disease is that they had what was, for all practical purposes, inapparent measles.

The proportion of inapparent to overt infection was higher in the groups of those who had received the larger doses of gamma globulin, although some inapparent cases occurred even when the small 1-ml. dose was used. A number of children who received the larger doses developed no antibodies during the epidemic period, but it is difficult to know if all these children were adequately exposed. The fact that susceptible children escaped infection during the summer epidemic in cottage 2 suggests that some children who received gamma globulin also would not have been infected.

The difference between antibody titers in the children with overt and those with inapparent infections raises the question of the solidity of immunity acquired in the absence of recognizable signs. The durability of this immunity can only be determined with the passage of time, but is sufficiency after a moderate interval was demonstrated by the five children who were reexposed seven months after their first experience with measles. These included three with low titers. Since some of the titers observed after inapparent disease were at the minimal level tested, and since these apparently gave protection against reinfection, it is possible that on occasion a child might never acquire antibodies that could be measured by the tests currently in use and yet might become immune.

The dependence of antibody titer on the severity of the disease is in contrast to the effect of poliovirus infections [12] but similar to the responses found after mumps infections.[13] The titers found after inapparent measles infections are similar to those in a normal population.[2] It may be that after inapparent infection the titers approach the value at which a semipermanent equilibrium is reached, without ever exceeding it. The equilibrium titer in these persons may be no lower than that which would have been attained under natural conditions in which there is an initial peak titer and a limited decline.

The failure to isolate virus from persons with inapparent infections is not in itself conclusive evidence of a low level of contagiousness. Techniques for isolation of measles virus are not yet sufficiently standardized and too little is known of the time at which specimens should be collected to allow a conclusion on the basis of purely negative results. However, taken together with the epidemiologic evidence there is a strong suggestion that gamma globulin reduces the contact spread as well as the severity of measles. The epidemiology of measles has been extensively studied and it is probable that if inapparent cases were fully infectious, they would have been recognized long ago.



Individual neutralizing titers in serums collected about five weeks after assumed onset of measles.

Many children receive several doses of gamma globulin on the occasion of several exposures to measles and never develop the disease. This may happen when the objective is only to modify the disease or when the child has a chronic illness and prevention is desired. It is likely that these children develop antibodies without overt disease and that the repeated administration of gamma globulin is unnecessary. In view of the high cost of gamma globulin and relative simplicity of the CF test for measles antibodies, a determination of CF titer might be valuable after the use of gamma globulin when no specific disease is observed. While more work is required to determine the exact correlation between CF titer and immunity, a titer of 16 or greater might tentatively be considered indicative of immunity. Facilities for carrying out such tests are not now generally available, but they could be added to any microbiological diagnostic laboratory without great difficulty.

Summary

Nineteen of 38 susceptible children who were exposed to measles and given gamma globulin developed measles antibodies without overt signs of disease. Five of these 19 children failed to contract measles when exposed again seven months later. Titers of antibodies acquired as a result of inapparent infection were generally lower than titers resulting from overt disease when serums were tested about seven weeks after infection. Epidemiologic evidence indicates that the inapparent infections were less contagious than unmodified cases. In order to avoid the needless readministration of gamma globulin on subsequent exposure, it is suggested that the complement fixation (CF) test might be used to determine the immune status of children exposed to measles who were initially considered susceptible yet remain asymptomatic after receiving a dose of gamma globulin.

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A POSSIBLE RELATION BETWEEN DISTEMPER IN DOGS AND MEASLES IN MAN.—The question of how closely related are the viruses of measles and distemper is an intriguing one. . . . Both agents propagate in either embryonating eggs or chicken cell culture, and dog kidney tissue culture or in suckling mice. Both produce a viremia, an apparently similar inclusion body, are relatively thermolabile viruses, and are of similar particle size. On the other hand, as evidence of their dissimilarity is the resistance of the ferret to measles infection and the failure of measles viral antigen to fix complement with potent canine-distemper-virus convalescent serums. It may be pertinent to mention also the apparent lack of pathogenicity of egg-adapted canine-distemper-virus for man. Certain broader questions, such as (1) whether measles infection in man is associated with canine distemper in domestic hosts, and (2) whether canine-distemper-virus vaccine will confer significant protection against measles, are in the forefront of other continuing investigations at the present time.—J. Warren, Ph.D., M. K. Nadel, Ph.D., E. Slater, A.B., and S. J. Millian, Ph.D., The Canine Distemper-Measles Complex: I. Immune Response of Dogs to Canine Distemper and Measles Viruses, *American Journal of Veterinary Research*, January, 1960.

THE INJURED KIDNEY

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From over 200 cases of suspected kidney injury, 84 proved cases were selected for analysis of diagnostic methods, management techniques, and sequelae. The degree of renal injury was classified according to radiographic findings as severe, moderate, minimal, or negligible. Diagnostic criteria included history of trauma, demonstrable hematuria, physical findings, and radiographic evidence. Retrograde pyelography proved diagnostic in 18 of 20 patients, while excretory pyelograms were diagnostic in 31 of 66 patients. Two patients died; 9 required renal surgery; 52 were followed 2 months or more; 5 developed hypertension as a consequence of renal injury, and in 9 cases there were persistent radiographic renal defects. The study indicates that radiographic classification of renal injury provides a key to clinical management, that most kidney injuries may be managed conservatively, that some renal injuries may result in permanent damage or hypertension, and that, if the complications of renal trauma are to be appreciated, persistent follow-up is essential.

Renal injury resulting from external trauma is quite common in today's society, the members of which are exposed to strenuous physical activity, contact sports, high-speed transportation methods, and unfortunately, a variety of lethal weapons. In any busy hospital accident room, traumatic injuries are frequently seen and a significant number of these may involve the kidneys. The social and industrial factors predisposing to renal trauma are so prevalent that the problem and its potential must be thoroughly understood by the practitioner, the surgeon, and the urologist alike.

It is the purpose here to present a series of 84 consecutive cases of authenticated renal injuries due to trauma, with an analysis of the diagnostic and management techniques employed. More than 200 Grace-New Haven Community Hospital records coded under renal trauma during the 10-year period from 1949 to 1959 were carefully examined in selecting these 84 cases, which meet the documentary requirements of proved renal trauma. An attempt has been made to classify these cases according to the severity of the lesions, and to correlate this classification with the clinical course and management on a statistical basis. The findings correspond closely to those in similar studies.[1] In addition, efforts at follow-up have been made in each case to determine the long-term sequelae of renal injury, with particular emphasis on renal function, hypertension, stone formation, anatomic deformity of the kidney, and changes in the character of urine.

Many authorities have recognized the vulnerability of the kidney to the trauma of external force as well as the less frequent involvement by perforating or penetrating injuries.[2] In the past three decades, many excellent reviews of renal trauma have appeared, each aimed at providing improved diagnostic techniques, classification, and management methods. Scholl and Ferrier,[3] in a summary of 220 cases of renal injury seen over a seven-year period at the Los Angeles General Hospital, have outlined the causes, incidence, character and severity, signs and symptoms, and operations performed. Some authors[4] have stressed the serious complications of untreated renal injury and advised the consideration of early exploration. Others[5] counsel caution and urge conservative measures in treatment. Harrison[6] stresses the importance of careful evaluation of total renal function prior to surgery in which nephrectomy might be indicated, and this is emphasized further by Lich[7] in his review of injuries to solitary kidneys. There seems to be no question that the management of renal injury can only be based on thorough knowledge of the exact nature of the injury, and a number of papers deal with the fine points in diagnostic techniques.[8]

Incidence

The peak incidence of renal trauma invariably occurs in the young adult group. It is reasonable that this should be so, since this age group is the one most often exposed to the forces which might bring about such trauma. Young men are more commonly injured than young women (table 1). There were 66 male and 18 female subjects included in our study. More than 50% of these patients were between 15 and 30 years of age. The occurrence of renal trauma decreases sharply after one reaches 45 years of age. There is apparently

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no statistical difference in the incidence of injury to the right kidney as opposed to the left. No cases of bilateral injury were recorded in this study. These observations correspond closely to those of Scholl and Ferrier who found the highest age incidence in the third decade, with men much more commonly affected than women.

Etiology

It is not surprising that automobile accidents account for a large number of renal injuries; 34 cases in this series were due to automobile accidents. A significant number of injuries were due to falls, both in the home, on icy streets, and as a result of occupational hazards, i.e., painters falling from scaffolds. In some studies, such falls account for the majority of renal injuries.[9] Athletic injuries accounted for 16 cases of renal trauma in this series. The sports most commonly associated with renal trauma are, of course, the contact sports (football, lacrosse, soccer, basketball, boxing, wrestling), and Kleiman[10] has demonstrated anatomic renal deformities resulting from prolonged exposure to athletic trauma. Alyea[11] has reported hematuria due to noncontact sports but this is thought not to be related to mechanical trauma. A small percentage of the cases reported here were due to direct blows in the kidney area, usually incurred in fights. There is only one perforating wound (gunshot) of the kidney in this series, while in other studies injury by gunshot, shrapnel, stabbing, and the like occur more often.

TABLE 1.—*Summary of Renal Injuries in Eighty-four Patients seen at Grace–New Haven Community Hospital 1949-1959*

Patients, Total		No.
Male		66
Female		18
		—
		84
Age Incidence		
Average age, yr.	27	
Youngest in series	5	
Oldest in series	80	
0-15 yr. of age		15
15-30 yr. of age		41
30-45 yr. of age		14
45-60 yr. of age		6
Over 60 yr. of age		5
		—
		84
Injury, Side		
Right		38
Left		46
Bilateral		...
		—
		84
Injury, Nature		
Automobile accident		34
Fall		27
Sports		16
Direct blow		6
Perforating wound		1
		—
		84
Pain Related to Renal Injury		
Localized pain in flank		60
Generalized abdominal pain		11
Chest pain		8
Colic		1
No pain		4
		—
		84
Other Injuries		
Fractures		22
Cerebral injuries		5
Visceral injuries		48
Multiple injuries, severe		12
Renal injury only		48
Interval After Injury Before Seen		
Range 30 min. to 10 yr.		
6 hr. or less		45
7 to 12 hr.		6
12 to 24 hr.		2
1 day to 1 wk.		22
1 wk. to 1 mo.		6
1 mo. to 1 yr.		1
More than 1 yr.		2
		—
		84

Findings Related to Renal Injury		No.
Flank or CVA tenderness		43
Generalized abdominal tenderness		21
Palpable flank mass		14
Absent bowel sounds		11
Fever		10
Local abrasions, lacerations		5
General Physical Findings		
Specific signs of renal injury		47
Nonlocalizing signs		26
Completely negative examination		11
		—
		84
Pattern of Pain and Hematuria		
Gross hematuria		44
With pain	41	
Without pain	3	
Microscopic hematuria		35
With pain	33	
Without pain	1	
Pain, with no hematuria		5
		—
		84
Laboratory Findings		
Gross hematuria		44
Microscopic hematuria		35
More than 50 rbc/hpf	18	
Less than 50 rbc/hpf	17	
No hematuria		5
Albuminuria greater than 1		17
Pyuria		2
White blood cell count more than 10,000/cc.		40
Initial hemoglobin level less than 13.5 Gm. or hematocrit value less than 40%		19
Subsequent drop in hemoglobin or hematocrit to normal levels		14
Blood urea nitrogen level more than 15 mg.% or nonprotein nitrogen more than 35 mg.%		13

Pathology

Many attempts have been made to correlate pathologic damage of the injured kidney with the clinical findings and symptoms. The usual pathologic-anatomic classifications are contusion, laceration, and fragmentation in varying degrees of severity. Histologically, the injured kidney may show a wide variety of lesions, ranging from simple intrarenal hemorrhage to complete fragmentation and necrosis of the kidney. The late result of renal injury may be complete healing, varying degrees of infarction with scarring, cystic degeneration (simple, hemorrhagic, calcified), hydronephrosis, pyonephrosis, or atrophy. Unquestionably, the long-term pathologic changes in the kidney are related to the severity of the initial injury, particularly as it relates to the blood supply. While the kidney cannot regenerate, it nonetheless tends to heal most traumatic injuries. The late results of pathologic changes in the traumatized kidney are discussed below.

Symptomatology

The patient suffering from renal trauma will almost invariably have pain in some degree. Only four patients in this series had no history of any discomfort. Localized flank pain occurred most commonly, but generalized abdominal or chest pain, and even renal colic, may be experienced by the patient. Very often the presence of multiple injuries, particularly rib fractures and visceral injuries, may obscure any frankly renal symptoms. The vast majority of patients suffering demonstable renal injury will also have hematuria, either gross or microscopic. Only five patients in this series were reported to have had no hematuria. Gross hematuria occurred in about one-half of the patients (table 1). Hematuria may be transitory and observed only on the first or second voiding after injury, or it may be prolonged for several hours or many days. In general, gross hematuria begins to disappear within a matter of hours after injury, even in the presence of severe damage, since the affected kidney may cease to function or clots may occlude the ureter on the affected side. In some cases the appearance of hematuria was delayed, having been overlooked by the patient initially, or perhaps having occurred as a late reaction. A majority of these patients in this study were seen within six hours or less after injury (table 1). Approximately 80% of this group was seen within 24 hours of injury, with an overall average of 6½ hours. Almost invariably the patients could relate their pain, hematuria, or both, to a definite episode of trauma. However, in some patients, especially children, the circumstances of injury were obscure. This was particularly true with contact sports. Many patients incurring renal trauma during sports activity completed the game or match before noting any difficulties. Parenthetically, it should be remembered that hematuria following minimal trauma may be the first sign of serious preexisting renal disease.[12]

Physical Findings

As outlined in table 1, associated injuries were frequent in the 84 patients with proved renal injury. About one-fourth of the patients suffered bone fractures, including 12 patients with multiple severe injuries. There were five patients with skull and central nervous system injuries and four with visceral injuries. However, over one-half of the series suffered only renal trauma as far as could be determined. Examination of patients with kidney injury usually disclosed flank or costovertebral angle tenderness, present in 51% of the patients reported here. Generalized abdominal tenderness occurred in about 25%, and about 17% of the patients in this series presented with a palpable flank mass. About one patient in eight, including those with visceral injuries, had absent bowel sounds. A significant number of patients had fever from slight to marked degree. Local abrasions and lacerations in the renal area were found in only five of the patients in this series. In summary, 47 of the 84 patients had specific signs of renal injury, 26 had nonlocalizing signs of general abdominal tenderness, and no signs of renal injury were elicited in 11 patients.

Diagnosis

Making the diagnosis of renal injury can be quite difficult, especially in the presence of an ectopic kidney[13] or other anomaly,[14] but generally depends upon four factors, namely, (1) a history of trauma to the renal area, (2) demonstrable hematuria, (3) positive physical findings, and (4) radiographic evidence. The criteria established for inclusion of patients in this series demanded the presence of at least two of these findings. A history of trauma in one renal area without any of the other supporting evidence is inconclusive, as would be any other single feature with the exception of incontrovertible radiographic evidence. Hematuria alone cannot be taken as evidence of kidney damage, since contusion of the bladder, ureter, or urethra with mucosal hemorrhage may also produce hematuria. Localized flank tenderness may be attributed to a variety of causes other than simply to renal trauma, and must be supported by other evidence of kidney damage. Definite radiographic evidence of renal injury is incontestable, of course. Table 2 summarizes the radiographic findings in the patients in this series. It is important to note that 39 of the 84 patients in the series showed no radiographic evidence of kidney damage. The techniques of history-taking, physical examination, and urinalysis are both fundamental and familiar. Initial laboratory study must include a blood count and hematocrit reading, as well as early determination of blood nitrogen and serum electrolyte levels.

TABLE 2.—*Summary of Radiographic Findings in Eight-four Patients with Proved Renal Trauma*

Patient Data	Patients, No.
Positive radiographic evidence of renal injury	45
No definite radiographic evidence of renal injury	39
	84
Plain radiogram of abdomen only	5
Intravenous urograms	66
Retrograde pyelograms	20
Cystograms	8
Evidence of renal injury apparent on plain x-ray of abdomen	11 of 79
Flank mass defined	7
Psoas shadow obliterated	6
Renal outline obscured	3
All three positive findings	4
Evidence of renal trauma apparent on intravenous urogram	31 of 66
Decreased contrast, delay, or nonfunction	15
Extravasation of medium	13
Incomplete filling of calyx or pelvis	9
Filling defects (clots)	5
Distorted calyceal pattern	5
Deviation or displacement of ureter	4
Kidney displaced by mass	3
Hydronephrosis	2
Evidence of renal trauma apparent on retrograde pyelogram	15 of 20
Extravasation of medium	15
Filling defects (clots)	9
Distortion of calyceal pattern	8
Kidney displaced by mass	2
Radiographic evidence of injury resolved completely	36 of 45
Persistent radiographic changes on follow-up	9 of 45
Radiographic evidence of diseased kidneys unrelated to injury	4
Renal calculi	2
Hydronephrosis, ureteropelvic junction obstruction	1
Atrophic pyelonephritis	1

Radiologic Techniques

Plain roentgenograms of the abdomen were the only radiographic studies performed in 5 patients in this study, while 66 of the 84 had excretory urography, 20 patients underwent cystoscopy and retrograde pyelography, and 8 cystograms were made. In the entire series plain roentgenograms disclosed evidence of renal injury only 11 times, a diagnostic incidence of only about 13%. A flank mass could be defined in seven of these patients; an obliterated psoas shadow was noted in six cases; the renal outline was obscured in three instances; and all three of these signs were noted in four patients. The excretory urogram was diagnostic of renal injury in 31 of the 66 patients examined, confirming the diagnosis in almost 50%. Diminished contrast, delayed function, or nonfunction of one kidney were most often noted by comparison with the opposite kidney; extravasation of medium was seen in 13 patients; incomplete filling of the kidneys or filling defect was frequently noted; and gross distortion of the calyceal pattern, displacement or deviation of the ureter, and displacement of the kidney was seen occasionally. Hydronephrosis was encountered once. The presence of shock unfortunately precludes the use of excretory urography because renal blood flow is reduced sharply and the medium will not be excreted in sufficient concentration. Retrograde pyelograms were made in patients with severe injuries who could not undergo excretory urography, and in those patients in whom confirmation of diagnosis was necessary. Retrograde pyelograms provided the most definitive diagnostic approach.[8a] Ninety per cent of the patients showed radiographic evidence of renal injury. In the 20 cases in which retrograde pyelography was employed, extravasation was noted in 15, filling defects in 9, and distortion of the calyceal pattern in 8 patients. Two patients showed marked displacement of the kidney by retroperitoneal hematomata.

TABLE 3.—*Classification of 84 Patients with Renal Injury According to Radiographic Evidence of Severity*

Degree of Injury	Patients, No.	Gross Hematuria	Microscopic Hematuria	No Hematuria	Positive Findings of Physical Exam.	WBC Over 10,000/Cc.	Decreased Hemoglobin or Hematocrit	Patients Operated On, No.	Patients Followed More Than 2 Mo.	Patients Developing Hypertension, No.	Patients with Persistent Radiographic Defects, No.	Immediate Deaths	Overall Complications, %
Severe	10	10	...	...	7	10	10	5	6	1	3	2	60
Moderate	20	17	3	...	10	13	6	4	8	2	3	...	25
Minimal	21	8	12	1	15	9	5	3	12	1	3	...	19
Negligible	33	9	20	4	15	8	3	1	16	1	...	...	3
Total	84	41	35	5	47	40	24	13	52	5	9	2	

The radiographic diagnostic tools to be used in determining the nature and extent of renal injury are specific and should be used promptly though judiciously; retrograde examination may induce infection, and should not be used routinely. Follow-up examination is also mandatory. In three-fourths of the patients in whom examination disclosed positive evidence or renal injury, follow-up roentgenologic examinations revealed complete resolution of damage, but nine patients had persistent radiographic abnormalities indicating permanent anatomic change as a result of injury. In addition to the effects of injury, four patients in this series were shown to have preexisting unrelated renal disease (table 2).

Classification

Because other factors vary widely (type of trauma, signs and symptoms), we feel that classification of renal injury is best made on a radiographic basis (table 3). The 84 patients presented here have been divided into four categories on the basis of radiographic findings, avoiding the usual categories of "contusion," "laceration," "fracture," "fragmentation," and "shattered kidney." Renal injuries are graded according to severity.

Grade IV: Severe Injury.—Radiographic evidence of retroperitoneal hemorrhage, extravasation, obliteration of psoas and renal shadows, or marked deformity of the collecting system is seen. The injured kidneys in this category are frequently nonfunctioning and must be examined by retrograde pyelography. This classification includes severely injured patients with fragmentation, fracture, and rupture of the renal pedicle. The patients in this classification also prove to be those with the most profound clinical signs of injury and those who must often come to operation. Deaths, persistent pyelographic changes, subsequent hypertension, and urologic surgery, comprising the major complications, are most common (60%) in this group (table 4).

Grade III: Moderate Injury.—In the category of moderate injury are included those patients with obscured psoas or renal shadows, nonfunctioning kidneys, or evidence of subcapsular hematoma, but without evidence of severe anatomic damage to the kidney. This category generally includes those patients in whom the degree of renal damage is fairly severe, but who do not usually require operative intervention. Prognosis for healing in this group is good. Associated clinical findings are not so striking as in the category above. Complications of persistent radiographic changes, hypertension, deaths, or necessary surgery are not frequent (table 4).

Grade II: Minimal Injury.—The minimal injury category includes those patients with intrarenal fracture of the kidney, and the radiographic signs include minimal distortion of the calyceal system, clots in the renal pelvis, delayed function, or decreased concentration of excretory media. It is noted in this category that gross hematuria is uncommon, that these patients usually require no operative intervention, and that the complications are minimal when encountered.

Grade I: Negligible Injury.—The negligible injury category includes all those patients in whom there is no radiologic evidence of renal injury. Hematuria, the cardinal finding, may be gross or microscopic, but is usually the latter. The vast majority of patients suffering renal injury are in this group. Complete, uncomplicated, spontaneous healing is almost the universal rule, and complications of renal injury are extremely rare.

Management

A great deal has been written about the management of the injured kidney. Opinions vary with the experiences of the authors. Colston[4] urges prompt operative intervention in one series of patients suffering from severe renal damage, while Sargent[5] stresses conservative management based upon his observation of healing of most renal injuries. The management must depend upon the clinical and radiological findings in each patient. The classification outlined above provides an excellent key to management. Those patients classified as having severe renal injury frequently will require operative intervention while those of moderate, minimal, or negligible degree of injury can most often be managed best by conservative measures. The classification of renal trauma presented above may well be helpful to ancillary medical personnel in determining the amount of observation and caution necessary in the care of individual patients. Attendants must be constantly alert to sudden, critical changes in the patient with "severe" renal damage, while those with "negligible" injuries may be served satisfactorily by standard care.

In general, immediate emergency exploration of the ruptured kidney is unwise.[8b] Perirenal hematoma is quite often self-limiting and the general clinical situation should be studied thoroughly before surgical exploration. There are four recorded cases in which injured solitary kidneys were removed.[6] Rupture of the renal pedicle is a critical condition and most often death will supervene before adequate therapeutic measures can be taken. However, a delay of several hours before operation in the usual severe renal injury is not dangerous and may be quite helpful in combating shock and determining the degree of associated injury. Other severe injuries usually take precedence over renal injury. Prompt neurosurgical intervention may be called for in cases of head injury, tracheotomy may be indicated on an emergency basis, exploration for ruptured intraperitoneal viscus may be necessary, and orthopedic evaluation with splinting of fractures may be expedient before renal exploration.

In this series 13 patients were operated upon with a total of 18 operative procedures (table 4). There were 11 urologic operative procedures including 3 nephrectomies, 3 renal explorations during the course of abdominal surgery, one heminephrectomy for fragmented kidney, one incision and drainage of an infected perirenal hematoma, and one exploration and drainage of a hemorrhagic cyst of the kidney. In addition, one patient was circumcised and one patient underwent suprapubic cystotomy; neither of these events related to the renal injury. There were seven nonurologic operative procedures in this group including two bowel resections, two tracheotomies, a splenectomy, repair of a lacerated liver, and one open reduction of

TABLE 4.—*Subsequent Course in Eighty-four Patients with Proved Renal Injury*

	Patients, No.	
Follow-up Period*		
No follow-up available	14	
Followed less than 3 mo.	26	
Followed 3 mo. to 1 yr.	16	
Followed more than 1 yr.	18	
	84	
Deaths in Series, Known		
As immediate result of renal injury	...	
As possible late result of renal injury	1	
As immediate result of multiple injuries	2	
Known subsequent deaths due to unrelated causes	4	
	7	
Blood Pressure Changes Related to Renal Trauma		
Initially normotensive	63	
Subsequently hypertensive	3	
With renal injury	2	
Without evident renal injury	1	
Remaining normotensive	60	
Initially hypertensive	11	
Subsequently normotensive	6	
Remaining hypertensive	5	
Initially hypotensive	10	
Subsequently normotensive	6	
Subsequently hypertensive	2	
Radiographic evidence of renal injury	1	
No radiographic evidence of renal injury	1	
Died of severe injuries	2	
Operations in Series†		
Patients operated on	13	Totals
Operative procedures	18	
Urologic operative procedures	11	
Nephrectomy	3	
Exploration during abdominal surgery	3	
Heminephrectomy	1	
Incision and drainage of perineal hematoma and abscess	1	
Exploration and drainage of hemorrhagic cysts of kidney	1	
Circumcision	1	
Suprapubic cystotomy	1	
Total nonurologic operative procedures	7	
Bowel resection	2	
Tracheotomy	2	
Splenectomy	1	
Repair of lacerated liver	1	
Open reduction of fracture	1	

* Average length of follow-up 11 mo.

† Not including cystoscopies, minor surgery, or closed reduction of fractures.

fracture. These figures do not include cystoscopic examination, minor surgical procedures such as suture of lacerations, or closed reduction of fracture.

Surgical Treatment

The type of surgical treatment rendered is dependent upon the nature of the injury. The completely shattered kidney demands nephrectomy and often the partially fragmented kidney must be removed. If, however, the fractured kidney can be repaired by heminephrectomy or but suture this may be the procedure of choice. Generally speaking, the kidney which is readily sutured would probably have healed spontaneously.[15] Viability of the remaining kidney tissue must be determined at operation by careful exposure and evaluation of blood supply.

The indications for surgical intervention include progressive or unresponsive shock, rising white blood cell count, or falling hematocrit, as well as any progression in radiographic evidence of damage. Perirenal hematomata are usually self-limiting and tend to stop bleeding by tamponade; they may be incised and drained as a late event. In this group, nephrectomy was accomplished within 24 hours in two patients and after 72 hours in a third patient. The heminephrectomy was delayed until the 16th day after the injury at which time the fragmented and nonviable portion of the kidney was found to be clearly demarcated. The hemorrhagic cyst which occurred was drained 48 hours after injury while the perirenal hematoma which became infected (presumably the result of retrograde ureteral catheterization) was drained on the 14th day after injury. Exploration of the injured kidney at the time of intra-abdominal surgery may be a simple and judicious maneuver. The posterior peritoneum can be opened easily, and the kidney may be palpated or viewed directly. The information thus gained will be extremely helpful in deciding upon the need for surgical therapy directed toward the kidney.

Conservative Management

The primary treatment of renal injury is bed rest. This study indicates that 80 to 90% of kidney injuries will heal with simple measures. It has been shown that early ambulation of a patient with renal injury of even minimal degree can result in secondary hemorrhage which may be disastrous. Supportive measures such as transfusion and antibiotics may be used as indicated. Hospitalization is necessary at least for a few days in order to determine the extent and progression of kidney damage. Gross renal function studies including phenolsulfonphthalein test, blood nitrogen determinations, and occasionally clearance studies may be in order. Hospitalization must be continued until the patient's condition is completely stable. Persistent follow-up examinations with adequate radiologic evaluation are also mandatory, since the late complication of renal trauma may be extremely grave. It has been stressed before, but cannot be overemphasized, that the management of renal injuries must be individualized to the patient.[16]

Sequelae

The late results of renal trauma are quite variable. Fortunately, the mortality due to renal trauma alone is low.[6] Much attention has been focused upon renal scarring, infarction, and atrophy as related to the later development of hypertensive vascular disease. This study was undertaken in large part to determine the incidence of hypertension in patients who had suffered renal damage. Seventy patients in this group were available for study with an average follow-up of 11 months. Fifty-two patients were followed for more than two months (table 3) and 18 patients were followed for more than one year. Nine patients who showed initial radiographic evidence of trauma continued to show permanent anatomic changes on subsequent studies.

In addition, an attempt was made to correlate subsequent hypertension with the original renal injury. Of the 63 patients who were normotensive when first examined, 3 developed hypertension. Two of these had evident renal injury as shown by radiography and one showed no radiographic evidence of renal injury. It is notable that 11 patients in this series were hypertensive when first seen, and 6 of these became normotensive subsequently; 5 patients remained hypertensive for periods of five months to four years. Ten patients were hypotensive or in shock when first examined; six of these subsequently became normotensive, and two patients died as a result of severe injuries not due primarily to renal damage. The remaining two patients in this group subsequently became hypertensive, one with radiographic evidence of permanent renal injury and one without demonstrable anatomic change. The criterion for hypertension was persistence of blood pressure readings above 150/90 mm. Hg.

While there were nine patients with persistent kidney defects radiographically demonstrable, none of them developed hydronephrosis. The nine patients with persistent renal injury included three with persistent calyceal distortion, two with persistent displacement of the kidney laterally, one with persistent renal cyst, one with lobulation of the kidney suggesting scar or infarct, one with surgical defect secondary to heminephrectomy, and one with renal atrophy. Both the patient with the atrophy and the patient with the infarct were hypertensive. Neither of these two patients were operated upon. There were no instances of urinary tract infection in the follow-up examination. Albuminuria, noted in

17 patients initially, persisted only in 4 patients, all of whom were hypertensive. Only one patient with hypertension showed no permanent albuminuria.

In this series there were no deaths directly attributable to renal injury. The two deaths which occurred in the immediate post-trauma period were due to multiple severe injuries and both of these patients had severe head injuries. There were four subsequent known deaths in the entire series. One patient died four years after renal injury as a result of hypertensive cardiovascular disease and a cerebral vascular accident. Since the hypertension did not predate the injury, it is suspected (though autopsy was not obtained) that renal infarction may have played a role in the development of the hypertension. Post-injury radiographic studies were not done and autopsy was denied in this patient; therefore no definite conclusions can be drawn. The other three deaths were from causes not relatable in any way to renal injury.

The subject of hypertension as a result of renal injury is receiving renewed attention. Persistent follow-up examinations of patients with renal injury will undoubtedly shed more light on the matter. At present, it would appear that relative or partial renal ischemia is a prime factor in the pathogenesis of urologic hypertension,[17] and if this is the case, we may expect that only those patients with rather extensive anatomic damage (scarring, infarction) will develop renal hypertension. Such a theory implies that the majority of patients suffering from renal trauma should not be subject to the subsequent development of renal hypertension, as noted in this series. Further experimental and clinical data relating renal injury and hypertension are necessary.

Summary

Renal injuries occur most commonly in automobile accidents, falls, and contact sports. Diagnosis is established by careful evaluation of the history, physical findings, urine examination, and urologic radiography. Classification, for therapeutic purposes, is best based upon urography. Treatment depends upon the clinical cause and by far the greater number of patients will require only conservative supportive management. Surgical exploration of severe injuries can very often be deferred long enough for thorough evaluation. Hurried emergency exploration of the patient with a suspected renal injury is generally unwise and frequently unnecessary.

While the vast majority of patients suffering from renal trauma will have no lasting ill effects, hypertension may occur as a result of the injury possibly due to anatomic deformity with subsequent physiologic malfunction. Other late effects of renal injury are rare but include scarring, infarction, cysts, calcification, hydronephrosis, and persistent infection.

All patients having sustained renal injury must have periodic follow-up studies for at least a year if late sequelae are to be corrected. These should include appropriate urologic radiography as well as gross and differential renal function studies as indicated.

Careful study of a large series of cases of proved renal injury reveals that the injuries may be classified according to the extent of damage evident radiographically. Such categorization also correlates very well with the clinical evidence of degree of injury, and provides a useful guide in the management of patients with kidney injuries.

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J.A.M.A., July 16, 1960

MANAGEMENT OF PATIENTS WITH ECZEMATOUS DISEASES

USE OF SOAP VERSUS NO SOAP

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This study includes 250 patients with eczematous eruptions. The four disease groups used were neurodermatitis, contact dermatitis (dermatitis venenata), infantile eczema, and eczematous hand dermatitis. These patients were used as subjects to determine whether ordinary use of soap would adversely affect their respective skin diseases while they were on a standard therapeutic regimen. The patients were given programs of therapy identical in all respects but one: the experimental group was allowed the use of soap for bathing and hand washing and the control group was not allowed the use of soap for any purpose. The clinical course of each patient was rated (as described below) at weekly intervals over a five-week period. A final statistical analysis of the eczematous patients who, respectively, used or did not use soap failed to reveal any significant difference between the clinical courses of the two groups.

The question whether the habitual use of soap on the skin has any favorable or unfavorable influence on the course of eczematous eruptions led to this study of 250 patients. Of these, 246 were available in a final assessment of over-all impression of improvement after five weeks of standard therapy. During this period, 124 had regularly used the same common brand of toilet soap for routine hand washing and bathing while the others had not. The four groups of patients (with neurodermatitis, dermatitis venenata, infantile eczema, and eczematous hand dermatitis) differed in their responsiveness to treatment, dermatitis venenata being the most responsive, and infantile eczema the most refractory, but in none of the four groups was there a significant difference between those who used the soap and those who did not.

Background

A good review of the problem of the uses of soap in dermatology is presented in "The Medical Uses of Soap."[1] In this publication the general belief that eczematous eruptions are intolerant to soap is elucidated. It is also stated that the alkalinity of soap makes the lesions of atopic dermatitis sensitive to its use.

Another review of the problem of eczematous hand dermatitis[2] points out that experience with, as well as the theoretical knowledge of the alkalinity, degreasing, and drying effects of, soap make it evident that soaps are harmful to hand eczema.

More recent articles express the opinion that some eczematous dermatoses are either always intolerant to use of soap or often intolerant to, or aggravated by, soaps.[3] It must be added that these views generally are shared by most dermatologists. There are, however, occasional dissenting voices[4] which indicate that soaps may play little if any role in the course of eczematous eruptions in man. Certainly, there is not complete agreement, and we were unable to find a record of a single controlled study which answers this question. The medical management of eczematous eruptions would be greatly simplified if patients were allowed the use of soap. It is time-consuming to explain to the patient that soap is dispensable, and this advice is almost invariably poorly accepted, to say nothing of inducing in the patient a negative attitude toward the entire management of his disease. Therefore, it was decided to initiate a broad statistical study, under controlled conditions, of the influence of soap in eczematous dermatitis while the patients were on a standard therapeutic regimen. The effects of soap were evaluated in patients undergoing active therapy, because this is the practical situation with which one is constantly confronted.

Method

The study was conducted for one year. Subjects were patients taken from the dermatology clinic of University Hospitals. During this year, patients with the following diseases were included in the study: neurodermatitis, contact dermatitis, hand dermatitis (without evidence of allergens), and infantile eczema. There was no selection of patients for the study; all patients who were admitted to the clinic with these eczematous diseases during the year were included. A random list was established for the order in which the arriving patients would receive the experimental or the control form of therapy.

As uniform a program of therapy as possible was adopted for all subjects, and all were observed

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over a five-week period. All subjects received a 1% hydrocortisone ointment and an emollient (Eucerin) cream for topical application. Adult subjects were given 30 mg. of phenobarbital three times daily and were instructed in the use of rubber gloves with cotton linings for dishwashing and routine houshold chores.

The infantile group (arbitrarily established for this study as consisting of patients with atopic dermatitis or neurodermatitis of any age up to puberty) was not given rubber gloves or phenobarbital. One-half the subjects in each group were not allowed the use of soap or similar cleansing agents, and the other half of each group were given a common toilet soap for routine hand washing and bathing and instructed to use this soap only for these purposes.

Table 1.—*Response After Five Weeks to Standard Treatment for Dermatoses of Patients Using or Not Using Soap*

		Disease									
		Hand Eczema		Neurodermatitis		Contact Dermatitis		Infantile Eczema		All Diseases, Average	
Period		Soap	No Soap	Soap	No Soap	Soap	No Soap	Soap	No Soap	Soap	No Soap
	No. of subjects	12	18	16	11	10	15	10	7	...	...
	Mean, $\bar{X}$	2.00	1.94	1.62	2.18	3.60	3.33	1.70	1.14	...	...
1	Variation of observations, σX^2	0.909	1.82	0.783	0.764	2.267	2.666	0.90	1.143	...	...
	Difference, D_1	0.06		−0.56		0.27		0.56		−0.0736	
	Variation of difference, σD^2_1	0.203		0.119		0.418		0.243		0.0504	
	No. of subjects	18	20	29	30	13	9	13	12	...	...
	Mean, $\bar{X}$	2.17	1.45	2.28	1.90	3.31	3.56	1.31	1.00	...	...
2	Variation of observations, σX^2	0.853	0.366	0.492	1.196	0.722	0.778	1.064	0.545	...	...
	Difference, D_1	0.72		0.38		−0.25		0.31		0.3557	
	Variation of difference, σD^2_1	0.063		0.058		0.139		0.150		0.0213	
1 & 2 Average											
	Weighted $\bar{D}_1$	0.5640		0.0720		−0.1203		0.4053		$D^*=0.2519$	
	Variation of $\bar{D}_1$, σD^2_1	0.0481		0.0390		0.1043		0.0927		$\sigma D^2=0.0150$	

* D=difference between soap and nonsoap groups for all categories of eczematous disease studied.

Table 2.—*Average Scores for Over-all Impression of Improvement of Dermatoses in Patients Receiving Standard Therapy While, Respectively, Using or Not Using Soap*

		Duration of Therapy					
		Start of Test		1 Wk.		5 Wk.	
Dermatitis	Use of Soap in Patients Receiving Standard Therapy	Score	No. of Subjects	Score	No. of Subjects	Score	No. of Subjects
Hand eczema	Yes	3.87	30	2.68	28	1.77	30
	No	4.13	38	3.14	37	2.45	38
Neurodermatitis	Yes	4.04	47	2.58	45	2.04	45
	No	4.00	44	2.79	43	2.02	41
Contact dermatitis	Yes	4.60	25	2.72	25	1.22	23
	No	4.71	24	2.87	23	1.29	24
Infantile eczema	Yes	3.96	27	3.09	23	2.54	26
	No	3.74	19	2.94	18	2.68	19
Average of all dermatoses	Yes	4.093	129	2.727	121	1.927	124
	No	4.136	125	2.934	121	2.115	122

A bag containing the medicaments and complete typewritten directions for use was given to each patient. In addition to the typewritten directions, the physician explained the details of the program at the time of the first visit.

A method of quantitating the severity of the lesions was established. This consisted of setting an arbitrary severity scale of 1 to 7 for each of six factors: erythema, scaling, oozing, crusting, pruritus, and vesiculation. For example, the mildest scaling was given the quantitative rating 1 and the severest scaling, the quantitative expression 7, the other numerical grades falling in between. In addition, an over-all impression of the eczematous process was quantitated on the same scale of 1 to 7. This over-all impression no doubt included all six factors listed as well as others in reaching a quantitative judgment. All these factors were quantitated at the time of the first visit and each subsequent week for five weeks, or a total of six visits. The patient's progress was not followed beyond the five-week period of this study.

The physician evaluating the lesions of a given patient did not know what therapy the patient was receiving. Four physicians participated in evaluating the subjects. Frequent checks, in which two physicians evaluated the same patient independently, showed that there was never more than a one-point difference in severity rating for any given factor, and usually the ratings for each factor were identical.

Only 12 of the 262 patients failed to complete the study. Six subjects in each of the two groups (soap and nonsoap) dropped out and were not included in the final evaluation. Because some patients failed to keep their appointments on the first or the fifth return visit, several of these particular recordings are absent (see tables 1 and 2). Because of the special attention the patients in this study received, only a limited number chose not to continue participation.

A statistical study was made to compare the change in severity of each disease category in the two groups (soap and nonsoap). Evaluations were made for differences after one and five weeks of therapy respectively.

Since observation of the first 70 patients established statistically that the over-all impression rating was an accurate index of the other six factors, the final statistical study was based on the differences in severity as judged from the over-all impression.

Results

An analysis of the variance of differences for the four dermatoses in 250 cases was interpreted as follows. 1. The data fail to show a significant difference between the soap and nonsoap groups in any, or all, disease categories (see tables 1 and 2). 2. An analysis of the differences between the disease categories in all subjects (both soap and nonsoap groups of patients), revealed that *(a)* there are significant differences among these four dermatoses with regard to patients' rates of recovery; *(b)* contact dematitis shows the highest and infantile eczema the lowest rate of improvement; *(c)* hand eczema and neurodermatitis are indistinguishable in rate of improvement scores; and *(d)* although all the curves are flattening out, there is evidence of slight continuing improvement in all groups of patients at the five-week observation point (see figure). 3. There was no significant difference in the rates of improvement of the diseases between period 1 (May to October) and period 2 (November to April). 4. The greatest improvement of the five-week period occurred during the first week (about 50% of the total five-week improvement).

Comment

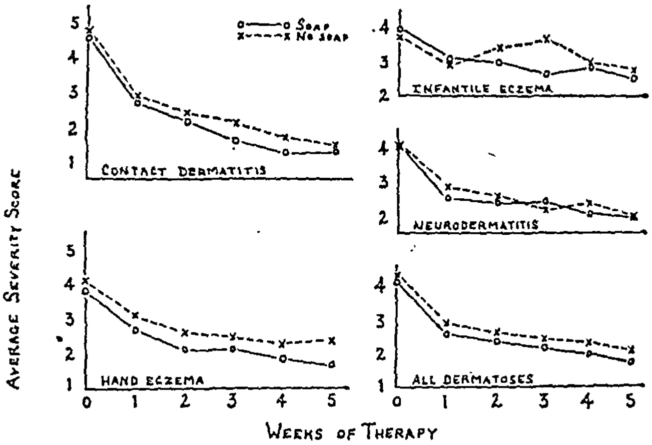
This study indicates that the use of soap for routine hand washing and bathing does not influence the course of these eczematous diseases while patients are on a standard therapeutic regimen. There has been considerable discussion regarding the adverse influence of soap on the eczematous diseases, but our study, under the conditions established, does not substantiate these claims. Because of the difficulty not only of explaining how to care for the skin without the use of soap but also of gaining the patients' acceptance of this routine in the treatment of eczema, it would seem of practical advantage to permit the use of soap in the management of patients with eczema without fear of adversely influencing the course of the disease.

We also believe that this study helps to delineate quantitatively the course of these eczematous diseases under therapy and that it serves as a model for quantitative evaluation of the course of eczematous diseases. From these quantitative data covering 250 patients with eczematous eruptions one can better predict the course of events during the first five weeks of therapy.

It is interesting that hand dermatitis responded to treatment almost exactly as did neurodermatitis with regard to rate of improvement. Infantile eczema was definitely the most recalcitrant, but this might reflect some neglect of therapy on the part of some parents of patients in our clinic group.

Summary

A controlled study and statistical analysis of 250 patients with four types of eczematous dermatoses (neurodermatitis, contact dermatitis [dermatitis venenata], infantile eczema, and eczematous hand dermatitis failed to show a significant difference in progress of the disease between groups using, respectively, toilet soap or no soap for bathing or washing. While the subjects were on a standard therapeutic regimen, these eczematous dermatoses studied over a five-week period improved at different average rates, which varied from about 25% for infantile eczema to about 75% for contact dermatitis. After five weeks of therapy the improvement rates were definitely lower than during the first week of therapy, and the greatest improvement rate was within the first week of therapy. There was no significant difference between the course of these diseases in winter and in summer.



Over-all impression of average severity score of dermatoses in patients using or not using soap while receiving standard therapy.

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Procter & Gamble Co., Cincinnati, supplied all the soap (Ivory) used in this study.

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SUDDEN AND UNEXPECTED DEATH IN EARLY LIFE

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Reduction of the incidence of sudden death in infants and children depends on prompter recognition, by parents and physicians, of significant symptoms and signs which have preceded such deaths in the past. The author presents an analysis of 17 unexpected deaths at ages ranging from 1 day to 30 months; seven cases are given in some detail. In many cases there was an infection that evolved into fatal septicemia within 48 hours after the first symptom. In three infants he only postmortem finding was mild to moderate pulmonary edema, and the patient had been in apparently normal health before being found dead in the crib. Thus, there remains a significant number of children for whom the precise cause of death cannot as yet be consistently determined.

In the period covered by this study, there were 189 pediatric deaths, of which 17 were classified as unexpected, at the Geisinger Memorial Hospital. This is an incidence of 9%. Stowens,[1] using more rigid criteria to define sudden death, reported an incidence of 4%. Despite this frequency the exact cause for death in a significant number of cases remains obscure even after the most careful postmortem examination.[2] This lack of satisfactory objective evidence concerning the cause of these deaths has led to such speculative explanations as suffocation by bedding,[3] lymphatism,[4] or status thymicolymphaticus.[5] It is the purpose of this discussion to review the cases of sudden death in the pediatric age group that have come to postmortem examination at the Geisinger Memorial Hospital in the past six and one-half years. The evidence gathered from this material indicates that usually, although not always, the cause of sudden death can be determined accurately. If the cause of death can be determined, many such deaths might be prevented.

Definitions and Criteria

"Sudden and unexpected death," as used in this study, has been defined by Adelson [2] as "the death of a child who was thought to be in good health or whose terminal illness appeared to be so mild that the possibility of a fatal outcome was not anticipated." These children were either moribund by the time cause for alarm was recognized, or they were found dead. Symptoms had not been present for more than 48 hours in any instance.

Methods

Cultures of the heart's blood were made within 10 minutes after the pronouncement of death in all cases. These cultures were made by adding 5 cc. of blood to 50 cc. of brain infusion broth and by adding 2 cc. of blood to 10 cc. of melted nutrient agar. At the same time, nose and throat cultures were obtained and plated on nutrient agar to which 5% rabbit's blood had been added. Anal swab cultures were performed by plating directly on Endo's medium, Shigella-Salmonella agar, and into tetrathionate broth, in that order. Also at this time, lumbar punctures were performed on all patients. The cerebrospinal fluids were examined for cell, protein, and sugar content. Within 30 minutes of obtaining the specimens, routine cultures for bacteria were done on all spinal fluids by inoculating the centrifuged sediment into brain-heart infusion broth with 2% rabbit's blood and by streaking the sediment on blood agar base plus 5% rabbit's blood. A complete autopsy including gross and microscopic examination was performed. Tissues were stained routinely with hematoxylin and eosin. Special staining techniques were used as indicated.

The clinical, laboratory, and necropsy findings were studied in 17 infants and children who died unexpectedly, according to the previous definition. The ages ranged from 1 day to 30 months, and about 60% were between 2 to 8 months of age. These deaths covered a six-and-one-half-year period from Jan. 1, 1953, to June 30, 1959.

Classification and Findings

Deaths in infants and children were categorized into the following four main groups, as modified after Farber [6] (see table): (1) congenital anomaly, (2) death from a known disease, (3) death of a child previously in good health but ill for less than 48 hours with disease which gave no cause for alarm, and (4) death of a child with no preceding sign of illness.

When this series of sudden deaths was carefully analyzed, it became apparent that eight of these children (47%) died of illnesses that, while they may have a certain mortality, ordinarily are considered curable. These children manifested symptoms ranging from 2 to 48 hours prior to death. If these symptoms had been recognized earlier as being significant, possibly several of these children could have been saved. On the other hand, certain conditions may prove utterly hopeless from the outset. To support these contentions, specific examples will be considered.

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Read before the Meeting of the Pediatric Society of Northeastern Pennsylvania, Oct., 1959.

Status Thymicolymphaticus.—There are few pathologists today who accept the so-called syndrome of status thymicolymphaticus as a cause for death. It was Carr;[4] in 1945, who repopularized this theory, proposing on the basis of weights and tracheal displacement that mechanical obstruction of the respiratory tract or liberation of a thymic lymph toxin was the cause of sudden death in cases otherwise unexplained. This work has not been corroborated. In 1932, Boyd[7] reported on the weight of the thymus gland in health and disease. In the first year of life, she found that median weight of the normal thymus gland was 19.5 Gm., with a range of 4.3 to 31.0 Gm. In the current series median weight of the thymus gland was 23.5 Gm., with a range of 4.4 to 60.0 Gm. The extreme high value of 60 Gm. was recorded in a 6-month-old infant who had a meningococcemia and bilateral adrenal hemorrhage. If this case is excluded, then the range of thymic weights in the first year of life is 4.4 to 38.0 Gm., which agrees more favorably with Boyd's figures.

Causes of Sudden Death in Children

Case	Age of Patient (Mos.)	Diagnosis
		Anomaly
1..........	1 day	Congenital heart disease
		From Known Disease
2..........	20	Nephrosis, ACTH therapy
11..........	2	Birth injury, intramedullary hemorrhage
		Previously Good Health (Symptoms 48 Hours)
3..........	2	Septicemia, meningococcus
4..........	3	Meningitis, pneumococcus
5..........	¾	Endocardial fibroelastosis
6..........	30	Croup caused by Hemophilus influenzae, type B
8..........	8	Pulmonary edema
12..........	6	Septicemia, meningococcus
13..........	2	Septicemia, meningococcus
14..........	¼	Septicemia, staphylococcus
15..........	1	Endocardial fibroelastosis
16..........	½	Endocardial fibroelastosis
17..........	8	Meningitis, Hemophilus influenzae
		Dead in Crib
7..........	4	Pulmonary edema
9..........	3	Pulmonary edema
10..........	8	Pulmonary edema (septicemia, staphylococcus; hypogamma globulinemia)

Farber,[6] after much experience in pediatric pathology, demonstrated that the gland was not diseased in any patient. Large glands were found without abnormal symptoms in many instances. The thymus varies in size more than any other organ and is largest during periods of rapid growth, which happens to coincide with the period of highest incidence of sudden death, the first year of life. It appears, therefore, that there is no justification for the diagnosis of status thymicolymphaticus.

Mechanical Suffocation.—There was no case of mechanical suffocation in this series. Those studies which have advocated this as a cause for sudden death have been poorly controlled. Abramson[3] reviewed 139 instances of sudden death in infants less than one year of age and, in the absence of any other findings, concluded that mechanical suffocation was the primary cause of death because 68% of these babies were found face down when dead. It is significant that no mention of postmortem findings was made in this study. On the other hand, Woolley[8] has actually measured the concentrations of carbon dioxide and oxygen found under bed clothing such as clothes and pillows. He was unable to measure concentrations low enough that might cause suffocation. In the British literature, Davison[9] reported on 318 cases of infants whose deaths, on the death certificates, had been attributed to suffocation. He was able to corroborate this diagnosis in only 25 cases, and in 18 of these mechanical suffocation occurred while the child was sleeping in bed with another person—so-called "over-lying."

Congenital Anomalies.—Many congenital anomalies are incompatible with life. There was one infant in our series of sudden deaths (see table) who died because of such a congenital anomaly.

Case 1.—A newborn boy appeared normal when examined at age 16 hours. Pregnancy and delivery had been normal. At age 20 hours, cyanosis and grunting respirations suddenly developed. Physical examination showed a cyanotic, flaccid infant who had grunting respirations. Heart sounds were of good quality. Liver was palpable three fingers below right costal margin. He deteriorated rapidly in a shock-like state and died at age 29 hours. Postmortem diagnoses were congenital heart disease, absence of coronary ostia and tricuspid and aortic valves, and hypoplasia of the right ventricle.

In a group of 365 neonatal deaths occurring in the first week of life, Claireaux[10] found that developmental defects were the cause of death in 34 infants. In his series congenital defects of the central nervous system accounted for about one-half of the total fatal abnormalities, while one-third were secondary to cardiac defects. It is of interest that the infant in case 1 appeared normal for the first 16 hours of life but thereafter went rapidly downhill. In a 20-hour-old infant, the triad of grunting respirations, cyanosis, and hepatomegaly is diagnostic of congestive heart disease. A roentgenogram of the chest and electrocardiography might be of diagnostic help. In this case a roentgenogram of the chest was performed and showed a normal cardiac silhouette. In any case digitalization and oxygen are indicated therapeutically. Surgical intervention carries an extremely high mortality and is only exceptionally indicated in cases of extreme pulmonic stenosis, tricuspid atresia, coarctation of the aorta, or patent ductus arteriosus.[11]

Sudden Death from Known Disease.—The following is a case from our series of sudden, unexpected death in a child who had a known disease and was receiving ACTH, an accepted form of therapy for that disease.

Case 2.—A 20-month-old boy developed the nephrotic syndrome three months prior to present admission. He responded to ACTH therapy by developing diuresis and losing 10 lb. (4.5 kg.). Edema recurred one day prior to current admission. He was hospitalized for a second course of ACTH. His own and family history gave negative findings. Physical examination showed an alert, active boy and gave negative results save for mild periorbital edema. Laboratory studies revealed the following information. Urine showed 1,000 mg. albumin and hyaline casts; cholesterol level was 378 mg.%; and other blood electrolytes and chemistries gave normal findings. He was given ACTH intravenously, 5 mg. q12h, parenteral penicillin, and streptomycin. Fourteen hours before death temperature rose to 103 F (39 C) due to no apparent cause. Two hours before death, he suddenly became cyanotic, was in a shock-like state, and had shallow respirations. He died despite vigorous resuscitative measures. Postmortem diagnosis was lipid nephrosis.

It is possible that death could have been iatrogenic. Good[12] has reported on serious untoward reactions to cortisone and ACTH. The incidence was 10% in 334 patients so treated. These reactions included severe electrolyte disturbances; convulsive seizures; severe infections including septicemia, pneumonia, abscesses, and peritonitis; duodenal ulcers with perforation and hemorrhage; severe emotional disturbances; pathological fractures; and others. Two unexplained sudden deaths occurred. In one case, the patient was found dead in bed, and in the second fever, shock, and death occurred without adequate explanation within four hours after the onset of mild illness. These circumstances are similar to those in our case. The alteration of resistance to infection that these agents induce is well known and is strikingly illustrated by the high incidence of death due to chickenpox in cortisone-treated children.[13] It is not proposed to discuss the hazards of steroid therapy, but, in the absence of any better explanation for the cause of death in this patient, it would seem that this case emphasizes the necessity for absolute indication and careful use of these agents.

Septicemia.—Among those patients manifesting symptoms of less than a duration of 48 hours, there were four cases of septicemia, representing an incidence of about 25%.

Case 3.—An 8-week-old boy developed a temperature of 104 F (40 C) 12 hours before admission. Two hours before admission purple spots appeared on the body. He was seen by his family physician, who referred him to the hospital. His own and his family history gave negative findings. Physical examination showed an infant who was moribund and in deep shock. He had scattered purpuric lesions, and his respirations were gasping. Heart sounds were faint and irregular. Anterior fontanel was normal. The infant died in the treatment room a few minutes after admission. Postmortem diagnoses were meningitis due to Neisseria meningitidis and Waterhouse-Friderichsen syndrome (fig. 1).

This case provides a classic and graphic illustration of the rapidity with which meningococcemia may progress. The recognition and treatment of this condition is a pediatric medical emergency second to none. Basic diagnostic procedures must be either rapidly performed or omitted until active therapy is in progress. Therapy includes immediate intravenous infusion of sulfisoxazole (Gantrisin) and hydrocortisone.[14] Unfortunately, however, there are patients who, like the boy in case 3, are beyond the help of the most vigorous therapy.

Case 4.—A 3-month-old boy developed fever of 101 F (38 C) two days before admission. He was given an *injection of penicillin*. One day before admission, he began to vomit and was lethargic. On the day of admission, he had persistent "twitching." His own and family history gave negative findings. Physical examination showed an unresponsive, severely ill boy who had an ashen color and a temperature of 103 F (39 C). Anterior fontanel was tense. In the hospital he died as spinal tap was completed. Spinal fluid was milky. Postmortem diagnosis was meningitis due to Diplococcus pneumoniae.

Often signs and symptoms of a dangerous illness are not recognized by either parents or physician. In another case of fatal meningococcemia, the mother gave the astounding history of how the baby vomited and was febrile at 1 a. m., was cyanotic and gasping at 4 a. m. (mother returned to bed), was found lifeless at 7 a. m., and a few minutes later was pronounced "dead on arrival" in the emergency room.

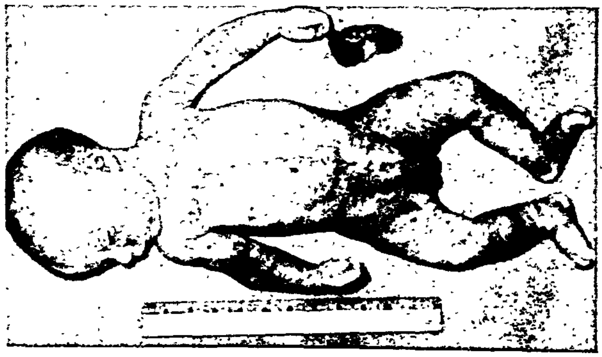

Fig. 1.—Eight-week-old infant dead from Waterhouse-Friderichsen syndrome. Note scattered ecchymosis and hemorrhagic adrenal gland.

Endocardial Fibroelastosis.—There were three instances of endocardial fibroelastosis, and the infants died within 48 hours after onset of first symptoms.

Case 5.—A 3-week-old-girl was in normal health until, four hours prior to admission, cyanosis suddenly developed. Labored, grunting respirations ensued and persisted to time of admission. Her own and family history gave negative findings. Physical examination showed cyanosis; grunting respirations; cardiomegaly; precordial systolic murmur, grade 3; and hepatomegaly. In the hospital she was treated for heart failure but died suddenly five hours after admission. Postmortem diagnosis was endocardial fibroelastosis (fig. 2).

The cause of endocardial fibroelastosis is not known, although numerous theories have been advanced. It occurs in 10% of patients with other types of congenital heart disease. The disease is invariably fatal; the onset of symptoms is usually about three to six weeks before death. Treatment is supportive and symptomatic, although Paul and Robbins[15] have reported on the introduction of talc into the pericardial sac. Of nine patients who were found to have primary endocardial fibroelastosis, six survivors were alive and improved from two and one-half to four years postoperatively.

Croup Caused by Hemophilus Influenzae, Type B.—Croup caused by Hemophilus influenzae, type B, is another dire pediatric medical emergency. The mortality is 10 to 20%.

Case 6.—A 2½-year-old boy vomited once eight hours before admission. Three hours before admission noisy respirations developed. One hour before admission respirations were rapid and shallow and the child looked pale and sick. He was seen by the family physician, who administered adrenalin and referred him to the hospital. His own and family history gave negative findings. Physical examination showed an acutely ill lethargic child; his eyes were slightly divergent, his temperature was 105 F (40 C), and his respirations were labored, 40 per minute, with subcostal and suprasternal retraction. He also had inspiratory stridor. In treatment room during admission examination, the child suddenly stopped breathing. Emergency tracheotomy was of no avail. Postmortem diagnosis was acute laryngotracheitis and glottic and supraglottic edema, due to Hemophilus influenzae, type B (fig. 3).

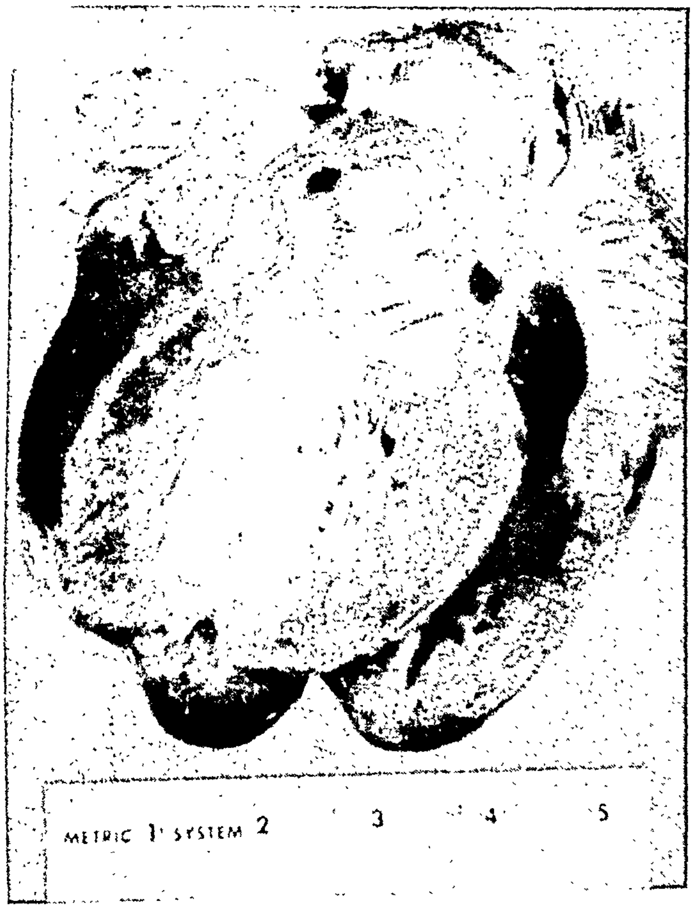

Fig. 2.—Endocardial fibroelastosis in 3-week-old girl who had nine-hour history of illness before death.

Hemophilus influenzae, type B, is different from the usual Hemophilus influenzae found in the nose and throat of healthy persons as it possesses a capsule. It has a definite invasive quality and is the etiological agent in numerous diseases of childhood, including Hemophilus influenzae meningitis. It has no relation to the influenza viruses. Sixty-five percent of cases occur in the three to seven year age group. The clinical course is marked by the short duration of obstructive symptoms, severe prostration which is out of proportion to the short duration of the illness, 100% incidence of a marked pharyngitis, and at least an 80% incidence of a red thick epiglottis.[16] A child with an illness of 8 to 12 hours duration, symptoms and signs of laryngeal obstruction, toxic in appearance, and with a red, edematous epiglottis can be assumed to have croup caused by Hemophilus influenzae, type B, until he is shown to have some other disease. The speed of therapy is of paramount consideration. It is directed toward relief of respiratory obstruction (tracheotomy) and specific therapy for toxemia and bacteremia (sulfadiazine or chloramphenicol, given intravenously, and possibly hydrocortisone, also given intravenously).

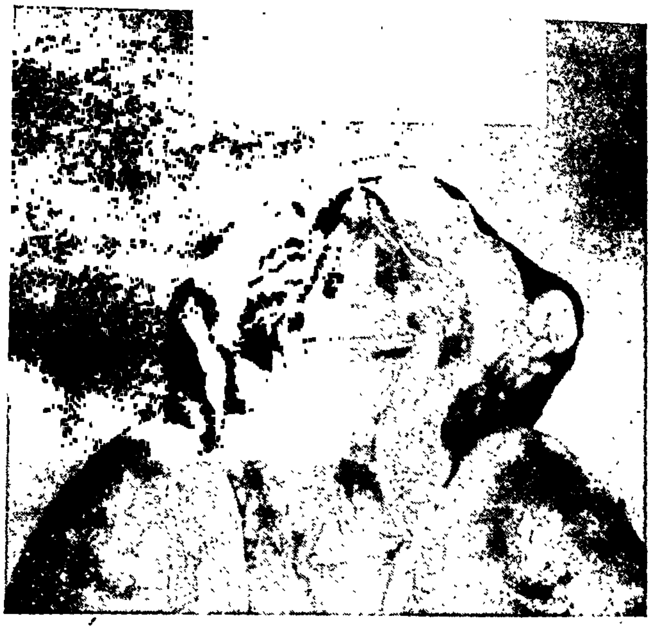

Fig. 3.—Larynx from 2½-year-old boy who had eight-hour history of illness before death. Note marked edema and inflammation of epiglottis and supraglottic area characteristic of croup due to Hemophilus influenzae, type B.

Infants Found Dead in Crib.—There remains a small group of infants for whom no completely satisfactory cause for death can be given. There were four such cases in this series. One infant (see table, case 8) presented rather minor and nonspecific symptoms of 48 hours' duration and then was found dead in his crib. No satisfactory bacteriological or anatomic cause for death could be found save for mild to moderate pulmonary edema and congestion. The remaining three infants had been in apparently normal health and unexpectedly were found dead in the crib. Pulmonary edema was the only abnormal anatomic finding in these three infants (see table, cases 7, 9, and 10).

Case 7.—A 4-month-old girl had taken a bottle normally and appeared well about five hours prior to admission. She was placed in her crib and was found apparently lifeless with her face down about five minutes prior to admission. The baby was pronounced dead on arrival at the hospital. Postmortem diagnosis was pulmonary congestion and edema. All cultures gave negative findings (fig. 4).

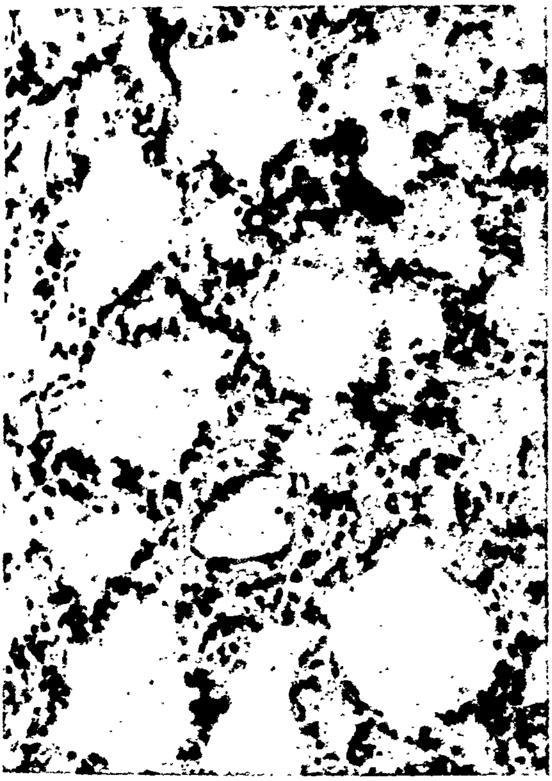
Fig. 4.—Pulmonary congestion and edema in 4-month-old infant found dead in crib.

It is this type of case that might formerly have been diagnosed as status thymicolymphaticus or as death due to suffocation. These conditions have previously been discussed. Other explanations that have been offered are chemical alteration in the tissues, constitutional anomalies, toxemia, abnormalities of calcium metabolism and glottic spasm, hypersensitivity to a variety of allergens, adrenal exhaustion, hypoglycemia, deficiency of the chromaffin system, and inadequate sympathetic nervous system.[17]

The more rigid the criteria used in defining sudden death, the fewer are the abnormal findings at postmortem examination. Minimal inflammatory changes in the respiratory tract or pulmonary edema or congestion are most frequently described in these cases.[18] The question might be brought up as to the significance of pulmonary edema and congestion in infants who died suddenly. Many of the other infants in this series in whom the cause of death was identified showed similar pulmonary changes. These changes were most frequently seen in the infants who died of proved cases of septicemia. Figure 5 shows the pulmonary changes in the infant in case 13 who was proved to have had meningococcemia. Is it that our bacteriological methods are not sensitive enough to pick up each and every case of sepsis? Stowens,[1] at the Armed Forces Institute of Pathology, has recently reported the pathological findings in 200 cases of sudden death limited strictly to those infants and children who had been completely asymptomatic prior to death. Only the lungs showed any alteration from the normal, the changes consisting of generalized overexpansion of the alveoli and of pulmonary edema. Stowens advances the hypothesis that death results from a generalized neural spasm mediated through the autonomic nervous system. The pulmonary effects of the reflex are probably not fatal and may be seen in infants who died from other causes. The reflex is a mass one, affecting all viscera, and most probably it is through the effect on the heart, either by arrest or by initiation of an abnormal rhythm, that death results. While such an hypothesis sounds quite logical, it can neither be proved nor disproved, nor does it completely answer the problem. The question still remains as to what initiates or causes this generalized neural spasm.

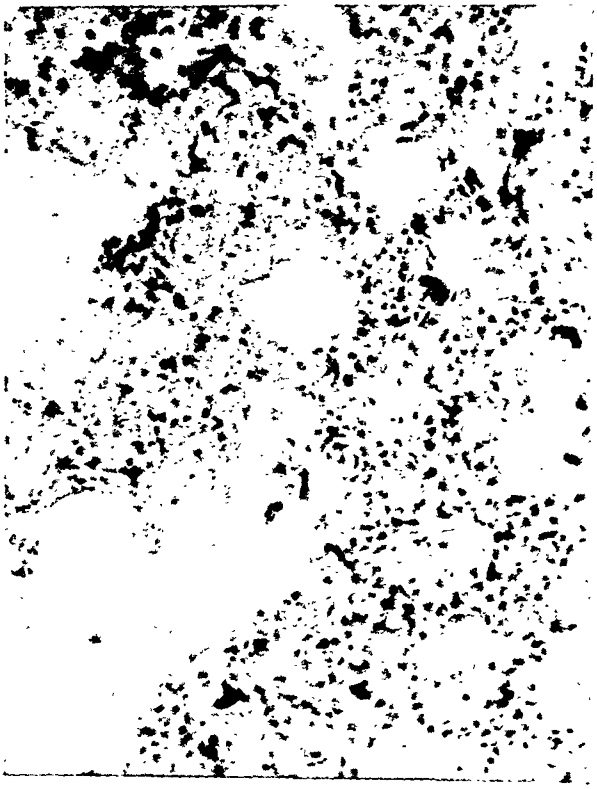
Fig. 5.—Pulmonary congestion and edema in 2-month-old infant who died suddenly from proved meningococcemia.

for rheumatoid factor became weakly positive, and eosinophilia was not present. The amount of productive sputum began to lessen, but on the seventh hospital day, the patient developed a thrombosis of the central artery of the right eye with permanent loss of vision. The patient's appetite improved within the next 10 days, and he was discharged while still continuing on therapy with methylprednisone and analgesics.

Second Hospital Admission.—The patient was readmitted to Hollywood Presbyterian Hospital in April, 1959, because of sudden weakness of the right arm and leg. At that time the hemoglobin level was 11 Gm.%. Results of urinalysis showed a trace of albumin, 10 red blood cells, and 10 white blood cells. The carbon dioxide combining power and sodium and potassium chloride levels were all normal. The sedimentation rate corrected to 22 mm. per hour. There was a reversal of the albumin-globulin (A/G) ratio. The L. E. cell phenomenon was absent on three preparations. Cold agglutinations were negative in all dilutions. Results of cephalin-cholesterol flocculation, serum transaminase, and cryoglobulin tests were negative. Sinuses were clear except for the right antrum (fig. 2A). The densities in the right upper lung field remained, but those in the left field were gone. Neurological examination revealed a right-sided wrist drop and a drop foot. There were no pyramidal signs.

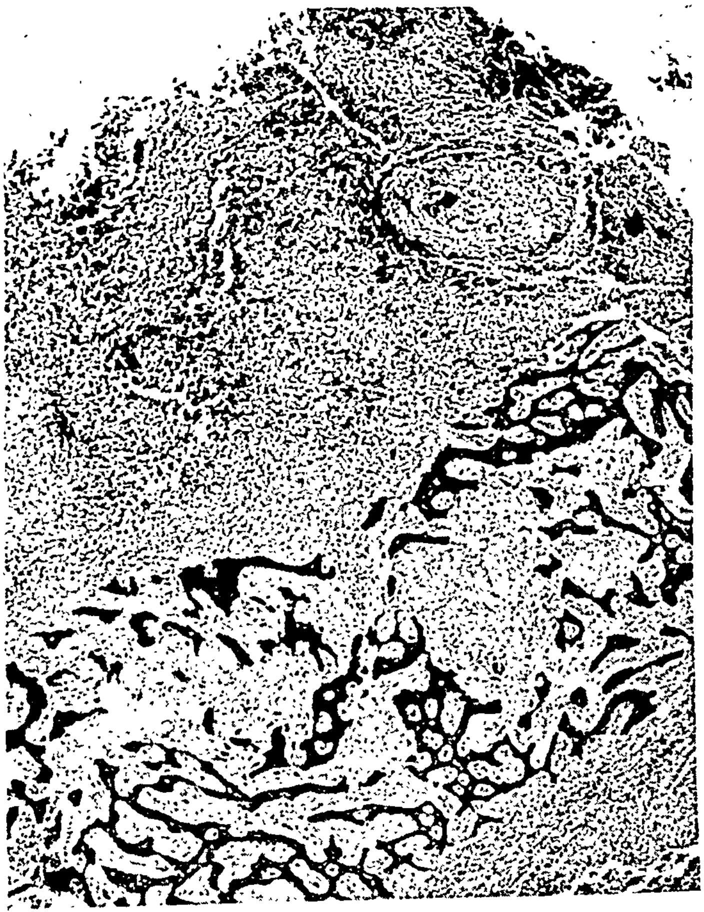

Fig. 5.—Photomicrograph of paranasal sinus, showing granulomatous surface with extension to involve bone. Large obliterated artery identified as margin of granuloma.

The paralysis in the right arm and leg improved rapidly, but the rheumatoid symptoms improved rather slowly. The patient was discharged 10 days after admission. He remained on therapy with analgesics, antibiotics, and methylprednisone in a decreasing dosage of 0.5 mg. every week.

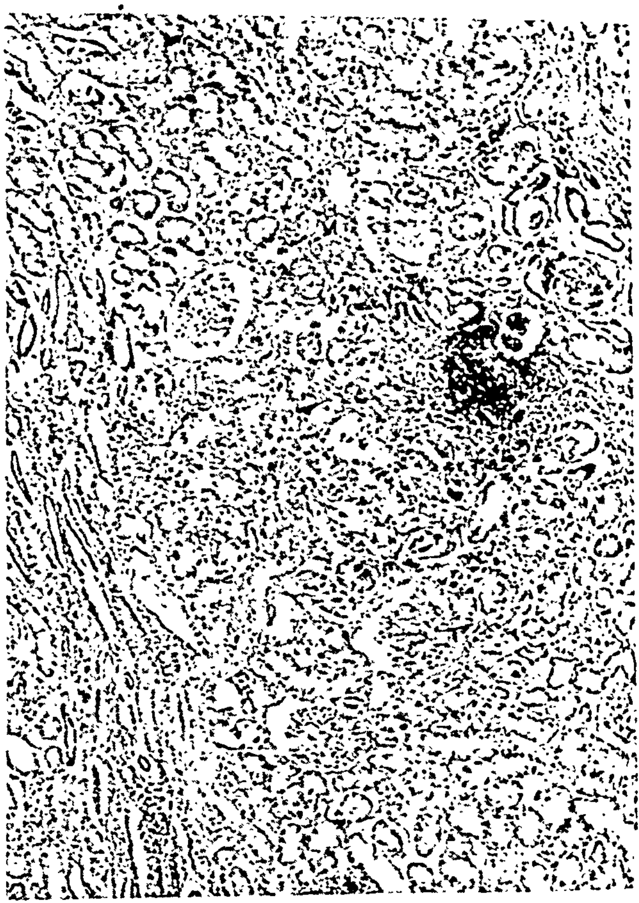

Fig. 6.—Photomicrograph of kidney, showing miliary granulomas in glomeruli.

During the next six weeks, until his final hospital admission, his rheumatoid symptoms improved, but his weight decreased. His cough became more productive and his nasal septum showed marked ulceration with large bloody crusts. There was no further obvious arteritis or vasculitis, but his general condition deteriorated.

Final Hospital Admission.—Final hospital admission was on July 6, 1959. At that time the patient had an intermittent foul bloody discharge from the nose, copious blood-tinged sputum, and some grossly observable blood in the urine. Temperature was 100 F (37.8 C), pulse rate 88 per minute, and respiration rate 24, but his blood pressure remained 130/80 mm. Hg. Roentgenogram of the chest revealed multiple nodular densities 2 to 3 cm. in diameter in both lung fields, two with cavitation (fig. 1C). Reexamination of the sinuses showed diffuse haziness throughout the ethmoid sinuses, with possible erosion of osseous structures and additional opacification of both maxillary sinuses (fig. 2B). Results of the Papanicolaou smears of the sputum were two negative ones for cancer cells and two reported to show squamous cell carcinoma. Six acid-fast smears were negative for pathological findings. At this time, one month before the patient's death, the diagnosis was changed from rheumatoid granulomatosis to Wegener's granulomatosis.

The A/G ratio continued reversed, results of the latex test became negative, and the nonprotein nitrogen level increased to 50 mg.%. The liver and spleen were palpable 1 to 2 fingerbreadths. There were loud, sonorous rales, inspiratory and expiratory, throughout both lungs. The nasal septum was perforated. The patient continued to be dyspneic and anorectic. Pyrexia increased, and he died on Aug. 8, 1959.

Postmortem Findings

Autopsy revealed that each lung was the site of about one-half dozen ovoid masses, ranging from 1.5 to 6.0 cm. in diameter. The bronchi were lined by granulomatous friable tissue. Microscopically, the pulmonary granulomatous nodules contained central necrotic tissue and exudate, with a granulomatous inflammation at the margins characterized by a mantle of mononuclear cells with histiocytes and many multinucleated foreign body giant cells (fig. 3-4).

The paranasal sinuses and nasal cavity had extensive granulomatous processes extending into the antrums and the ethmoid and sphenoid bones. The nasal septum was destroyed. There was extensive bone destruction and inflammation involving the orbits, with complete disruption of the medial wall of the right orbit. The optic nerves were surrounded by inflammatory exudate. The bone of the sella was partly destroyed, but the pituitary was intact. There was no involvement of the brain. The nasal sinuses microscopically showed granulomatous inflammation and necrosis, with occlusive vascular lesions (fig. 5).

The kidneys had small, miliary granulomatous foci in the cortex and medulla which were frequently centered about glomeruli showing hyaline degeneration of both capillary basement membrane and pericapsular collagenous tissues (fig. 6). The spleen was enlarged, weighing 400 Gm. (13.3 oz.), and, microscopically, many miliary granulomas were found principally related to the trabeculae and capsule.

Comment

This patient had most of the clinical features of Wegener's granulomatosis including severe rhinitis and sinusitis, hemoptysis, hematuria, hyperglobulinemia, peripheral neuritis, and vascular thrombosis. There were no skin lesions. Pathologically, the giant cell granulomatous lesions destroyed the nasal septum, the medial wall of the right orbit, and the bone of the sella. The pulmonary, renal, and splenic necrotizing granulomatous lesions and vesiculitis were characteristic.

Wegener's granulomatosis is an uncommon triad of unknown etiology, differing clinically and pathologically and in character and distribution of lesions from similar conditions such as malignant granuloma and polyarteritis nodosa. Although many authors have believed it to be a manifestation of hypersensitivity, the etiological mechanism is obscure. Wegener's granulomatosis appears to have the common histological abnormality of "fibrinoid change" found in collagen diseases, seen in the wall of the blood vessels or in the connective tissue proper.

Summary

A case fulfilled the criteria for a diagnosis of the clinicopathological triad of Wegener's granulomatosis. This disease is characterized by necrotizing giant cell granulomatosis of the upper respiratory tract and lungs, necrotizing vesiculitis of the small arteries and veins, and focal glomerulonephritis. The duration of the patient's illness was one year and three months. The disease was clinically diagnosed *one month ante mortem*. The clinical course began with intractable rhinitis and sinusitis which was unresponsive to antibiotic therapy. Steroid therapy appeared to cause a five-month remission. This was followed by nodular infiltrates of the lungs with cavitation, arthralgia, peripheral neuritis, debilitation, and loss of vision of the right eye. Progressive renal failure then ensued.

133 S. Lasky Dr. (Dr. McDonald).

Drs. John Budd and Joseph Davis, of the Department of Pathology, Hollywood Presbyterian Hospital, Los Angeles, assisted in this study.

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J.A.M.A., July 16, 1960

RENAL FAILURE SECONDARY TO ETHYLENE GLYCOL INTOXICATION

Robert I. Levy, M.D., Baltimore

A 36-year-old man was admitted to a hospital in a stupor with a history of six days of oliguria after a period of heavy alcohol intake. He complained of headache and of tenderness bilaterally in the costophrenic angles. He underwent dialysis by means of a twin-coil kidney twice, with evidence of improvement each time. He remained lethargic, however, continued to void less than 20 ml. of urine per day, and died in coma on the 17th day of oliguria. Autopsy findings included the presence of birefringent crystals of calcium oxalate in many of the kidney tubules; this is diagnostic of ethylene glycol intoxication.

Ingestion of ethylene glycol is an uncommon cause of acute renal insufficiency. In the case to be reported, acute renal failure was the presenting problem. Although a nephrotoxic agent was suspected, the precise causative agent was not established until postmortem examination. In retrospect, ethylene glycol could have been clinically suspected, since this patient's course closely followed that documented in the literature for this particular nephrotoxic agent. Central nervous system signs, such as convulsions or coma, have often been reported to precede the onset of oliguria. During the course of renal insufficiency from ethylene glycol ingestion, the early development of metabolic acidosis and marked tenderness in the costovertebral angle have been particularly striking in the cases reported. The absence of pulmonary symptoms until late in the course of renal insufficiency was an atypical feature in the case reported below.

Report of a Case

A 36-year-old man was transferred from Lutheran Hospital to Sinai Hospital on the sixth day of acute renal insufficiency. The patient had been an alcoholic for two years prior to admission. He had been drinking heavily on New Year's Eve and on Jan. 2.

Physical examination revealed him to be in a stuporous condition. The white blood cell count was 39,000 per cubic millimeter, with a differential count of 75% segmented neutrophils, 19% juvenile neutrophils, 5% lymphocytes, and 1% monocytes. Results of urinalysis were specific gravity 1.010, acid reaction, and albumin content 3+; microscopic examination revealed numerous red blood cells per high-power field; no crystals were noted. A lumbar puncture revealed an initial pressure of 275 mm. H_2O. The fluid was clear, containing 75 mg.% of protein, 14 red blood cells per cubic millimeter, and no white blood cells. The patient regained consciousness after about 24 hours, and on the second hospital day (the third day after the reported heavy alcohol intake) he voided 350 ml. of urine. The next day the urine output was 65 ml. The patient had a tarry stool and complained of a headache, as well as bilateral tenderness in the costovertebral angles. The urinary output during the third to sixth hospital day was less than 50 ml. per day. The blood urea level gradually rose to 235 mg.% by the sixth hospital day and that of bicarbonate (alkali reserve) was 10 mEq. per liter. The patient was transferred to Sinai Hospital for further management.

At the time of his admission to Sinai Hospital, the patient's temperature was 99 F (37.2 C), pulse rate 72 per minute, respiration rate 24 per minute, and blood pressure 150/90 mm.Hg. He complained of bilateral flank pain, had occasional hiccup, and vomited several times during the examination. The skin hydration was good, and the eyes were slightly puffy. While the heart was not enlarged, there was a forceful impulse at the apex in the fifth intercostal space in the left midclavicular line and a soft apical systolic murmur. The pulmonic second (P_2) was greater than the aortic second (A_2) sound. There was marked bilateral tenderness of the costovertebral angles. The patient was alert and cooperative. The hematocrit reading was 36.5%, white blood cell count 17,500 per cubic millimeter, with a differential count of 83% segmented neutrophils, 2% juvenile neutrophils, 20% lymphocytes, and 5% monocytes. Urinalysis revealed a specific gravity of 1.010, protein content of 4+, alkaline reaction, and no sugar. Microscopic studies revealed numerous red blood cells, five to six white blood cells per high-power field, and occasional granular casts. Blood chemistry studies gave the following values: blood urea 324 mg.%, bicarbonate (alkali reserve) 10 mEq. per liter, serum potassium 5.6 mEq. per liter, serum sodium 129 mEq. per liter, serum chlorides 90 mEq. per liter, blood creatinine 21 mg.%, serum calcium 9.9 mg.%, and serum inorganic phosphorus 9.6 mg.%. Electrocardiographic findings were within normal limits.

During the first three days in hospital the patient complained of headache and had occasional episodes of retching and vomiting. On each day he passed less than 20 ml. of urine. On the ninth day of oliguria (the third day in Sinai Hospital) the patient was more drowsy. He was given only 500 ml. of fluid per day containing 20% of glucose, and rectal enemas containing carboxylic acid resins in the sodium and ammonium cycle were given to combat the hyperpotassemia. Chloramphenicol and vitamins were also given.

From the Department of Medicine, Sinai Hospital.

On the 10th day of oliguria there was a prominent precordial heave, the left heart border being percussible just inside the anterior axillary line; rales were audible at the lung bases. The patient was digitalized. At this time the blood urea level was 424 mg.%, serum potassium level 7.1 mEq. per liter, and bicarbonate (alkali reserve) level 7.0 mEq. per liter. The patient was subjected to dialysis by means of a twin-coil kidney the next day, with marked improvement in symptoms and blood chemistry. Evidence of heart failure disappeared, but the costovertebral tenderness remained as prominent as before and the urinary output remained less than 10 ml. per day. Fluid intake was restricted more vigorously than before.

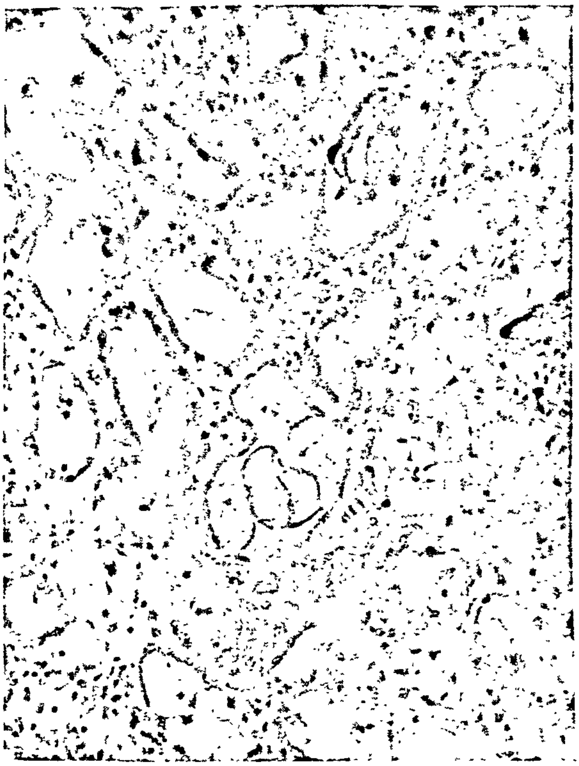

Fig. 1.—Photomicrograph: section of kidney, showing striking vacuolization of tubular epithelium and presence of calcium oxalate crystals in dilated lumen.

On the 15th day of oliguria, because of evidence of hyperpotassemia, the patient was treated with administration of hypertonic glucose and insulin, sodium lactate, and calcium gluconate. The next day, the 16th day of oliguria, the patient was subjected to dialysis for the second time, with good chemical evidence of improvement. He remained lethargic, however, and the urinary output continued to be less than 20 ml. per day. Numerous rhonchi appeared throughout the chest, with bilateral rales at the bases. On the 17th day of oliguria the patient became comatose and died.

Autopsy Findings.—Numerous petechiae and larger areas of hemorrhage were present in the skin and mucosa of the gastrointestinal tract. The lower lobes of the lungs contained areas of bronchopneumonic consolidation. The kidneys were swollen, each weighing 270 Gm. (9.5 oz.). The cut surfaces were glistening and moist. The surface of the brain appeared edematous.

Sections of the kidneys showed striking alterations (fig. 1, 2, and 3). The proximal convoluted tubules were dilated, the epithelial lining being either flattened or strikingly vacuolated. Many tubules contained birefringent crystals of calcium oxalate which are diagnostic of ethylene glycol ingestion. Sections of the brain merely showed perivascular collections of lymphocytes.

Comment

The shortage of glycerol during World War I aroused interest in the role of glycols as solvents for drugs. Early papers minimized the potential toxic effects of ethylene glycol.[1] However, numerous papers that followed during the 1930's discussed the pharmacology and toxicology of various glycols and gave every indication and warning of their potentially toxic effects.[2] These reports followed closely after the first report of two deaths resulting from the ingestion of ethylene glycol in 1930 published in Queries and Minor Notes in The Journal.[3] Death occurred early in these first two cases, central nervous system and pulmonary symptoms predominating before acute renal insufficiency developed. The first complete, well-documented clinical instance of poisoning by the glycols was reported in 1937 by Geiling and Cannon[4] as the

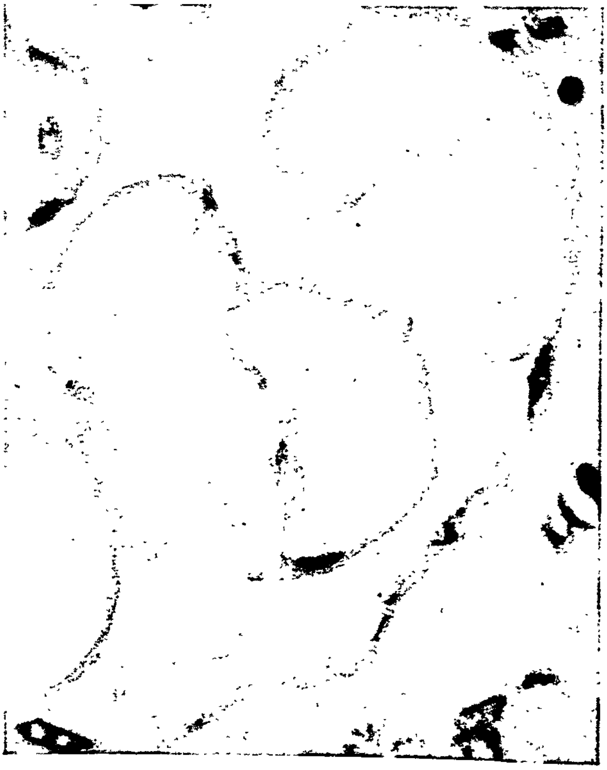

Fig. 2.—Photomicrograph: section of kidney, showing detailed appearance of calcium oxalate crystal in tubular lumen.

"elixir of sulfanilamide tragedy." In this instance diethylene glycol was used as a solvent for sulfanilamide and hepatotoxicity was a prominent feature. Since that time the ingestion of ethylene glycol, imbibed as antifreeze, has provided the material for numerous reports, often of fatalities.[5] Recovery has been reported in persons who ingested a small quantity of ethylene glycol, usually less than 100 ml.,[2a] but death during the initial phase of central nervous system signs or during the course of acute renal insufficiency has been more common. A summary of the reported cases is given in table 1.

Fig. 3.—Photomicrograph: section of kidney, showing birefringence of calcium oxalate crystals when observed with polarized light.

TABLE 2.—*Comparison of Glycols and Oxalic Acid*

	Glycols			
	Ethylene	Diethylene	Propylene	Oxalic Acid
Formula	CH_2OH CH_2OH	CH_2OH CH_2 O CH_2 CH_2OH	CH_3 $CHOH$ CH_2OH	$COOH$ $COOH$
Source	Antifreeze	Solvent for "elixir of sulfonamide" tragedy[4]	Common vehicle for drugs	High content in certain foods
Metabolic product	Oxalic acid	Not converted to oxalic acid	Pyruvate, glycogen	Metabolically inert
Toxicity	Cerebral, pulmonary, renal	Central lobular hepatic necrosis, nephrotoxic, "chemical nephrosis"; absence of calcium oxalate crystals in renal tubules	Relatively nontoxic	Nephrotoxic in large amounts; hypocalcemia

Relation Between Ethylene Glycol and Oxalate Metabolism.—The pathology of ethylene glycol poisoning is intimately related to the toxicology and metabolism of oxalates. Early studies of the glycols in the German literature indicated that oxalic acid was an end-product in the metabolism of ethylene glycol.[6] These studies need to be repeated by means of modern methods of biochemistry and enzymology to identify more precisely the location, rates of reaction, and enzyme systems involved in the biological oxidation of ethylene glycol to oxalate. It has not been established whether the oxidation occurs exclusively in the liver, or whether the reaction can take place in situ in the renal tubular cells. Perhaps it would not be too unreasonable to suspect that alcohol dehydrogenase is the enzyme responsible for the initial oxidation to an aldehyde, but preliminary studies indicate that such a reaction in vitro proceeds at a slow rate. Pyridoxine deficiency has recently been reported to result in the deposit of calcium oxalate crystals in the renal tubular lumen.[7]

TABLE 1.—*Summary of Cases of Ethylene Glycol Poisoning Reported in the Literature*

	Cases	
Source	No.	Type
Queries and Minor Notes,[3] 1930	2	Ethylene glycol (Prestone) ingestion: death after 12 hours due to respiratory failure and convulsions
Brekke,[5d] 1930	2	Recovery from renal decapsulation after initial symptoms resembling alcohol intoxication
Geiling and Cannon,[4] 1938	2	Diethylene glycol poisoning: renal and hepatic lesions
Boemke,[5e] 1943	2	Accident in German Army, when bucket of antifreeze was substituted for water in coffee. Author first to ascribed death to oxalate deposit in kidneys
Milles,[5f] 1946	1	Central nervous system (CNS), pulmonary, and cardiac symptoms: death in 22 hours; oxalate crystals in the urine
Pons and Custer,[5b] 1946	18	All died within 3 days. Intracranial lesion: meningoencephalitis. Minimal renal tubular damage, but crystals of calcium oxalate present
Hagemann and Chiffelle,[5c] 1948	3	All died in early stage of CNS symptoms. Severe acidosis within 6 hours, with early minimal rise of BUN
Kahn and Brotchner,[5g] 1950	3	One survival after ingestion of 240 ml. of ethylene glycol
Berman, Schreiner, and Feys,[5a] 1957	2	Mild cases, with survival after ingestion of about 90 ml. of ethylene glycol; diagnosis confirmed by needle biopsy

Studies on the pathology of oxalic acid poisoning strongly suggest that it is a potent renal tubular toxin. The studies of Dunn, Hayworth, and Jones[8] clearly indicated that oxalic acid causes rapid damage to the proximal tubular cells, before crystals of calcium oxalate appear in the tubular lumen. In these studies of Dunn and co-workers, doubly refractile crystals were widely distributed in the proximal convoluted tubular cells without evidences of tubular blockage by the crystals of calcium oxalate. This suggests that the oxidation of ethylene glycol to oxalate and the latter's direct toxic action on the proximal tubular cells represents the mechanism of renal toxicity. Such localization is similar to that of two more common nephrotoxic agents, carbon tetrachloride and mercury. The characteristic pathological feature of calcium oxalate crystals plugging the tubular lumen is of diagnostic value but probably has little pathophysiological significance.

On the other hand, the initial neurological manifestations may be due to ethylene glycol itself, rather than to oxalic acid. These symptoms occur within 30 minutes of ingestion, and it is unlikely that the oxidation product, oxalate, could be responsible. Furthermore, central nervous system symptoms are not reported as a striking feature of oxalate poisoning.[9] Pons and Custer [5b] suggested that ethylene glycol resembles ethyl alcohol in its absorption and distribution and that the oxidation product, oxalate, is formed in situ in brain and kidney. A comparison of various glycols and oxalic acid is given in table 2.

As shown, those glycols having an ether linkage, such as diethylene glycol, produce central necrosis of liver lobules as well as vacuolization of renal tubular cells. Crystals of calcium oxalate are not found, and oxalate is not an end-product of the metabolism of these glycols. Furthermore, severe acidosis is not a prominent feature of the clinical course of diethylene glycol poisoning.[4]

Congenital oxaluria may result in the formation of renal calculi with the late development of chronic renal insufficiency, but in spite of increased oxalate in the urine, the development of acute renal insufficiency is not a characteristic feature of the syndrome. Undoubtedly, the sudden exposure of the renal tubular cells to a large concentration of oxalate, as in exogenous oxalic acid or ethylene glycol poisoning, is an important factor. The fatal dose of oxalic acid has been estimated to be as low as 2 Gm.[8] Berman, Schreiner, and Feys [5a] calculated that, if 100 ml. of ethylene glycol is considered a fatal dose, and if 3 to 10% is converted to oxalic acid, the fatal dose of oxalic acid is potentially available. This begs the question of the rate of oxidation of ethylene glycol and leads to further speculation about its mode of excretion by the kidney. It is attractive to speculate that oxalate is secreted by proximal convoluted tubular cells and chelates intracellular essential divalent metals, calcium, or magnesium, leading to necrosis of the cell.

Treatment of ethyene glycol poisoning at present remains supportive. The suggestion that administration of calcium or parathyroid extract (Parathormone) might be effective is unsound, since it is based on the assumption that hypocalcemia is produced by ethylene glycol. Hypocalcemia is not an early clinical feature of ethylene glycol poisoning, as it is with oxalic acid poisoning. If the oxidation to oxalic acid could be prevented early the toxic effects on the kidney could be eliminated, but the effects on the central nervous system would probably not be affected. Chelating agents, such as ethylene diamine (Versene) would not seem helpful. Treatment during the stage of acute renal insufficiency demands the same careful attention to details of clinical management and dialysis when indicated as do other causes of acute renal insufficiency. Ingestion of ethylene glycol will continue to result in occasional cases of acute renal insufficiency as long as ethylene glycol remains a cheap, readily available, and effective antifreeze.

Summary

The case of ethylene glycol intoxication reported was characterized initially by central nervous system signs and later by acute renal insufficiency. The patient died after supportive therapy and two dialyses. It is suggested that ethlyene glycol itself is responsible for the initial central nervous system effects and that oxalate is responsible for the acute renal insufficiency. When oxalate is concentrated within the renal tubular cell, it possibly binds some essential intracellular divalent cation, leading to tubular degeneration.

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Dr. T. Weinberg performed the pathological studies.

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J.A.M.A., July 16, 1960

VARICELLA BULLOSA

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Formation of bullae is considered a rare variation or manifestation of chickenpox. Textbooks of medicine or pediatrics either do not mention it or merely note its rare existence. Wishik and Bullowa,[1] in reporting surface complications of varicella among a total of 2,534 patients, made no mention of bullous varicella. Rolliston, in discussing a fatal case of bullous varicella described by Gordon[2] in 1927 stated, "The bullous character of several of the lesions is undoubtedly the most remarkable feature of the case as varicella bullosa is the rarest form of chickenpox. Not only have few examples been recorded in the literature but the condition appears to be unknown to pediatrists of long and wide experiences." Apparently the term varicella bullosa was first used in 1819 by Cross[3] of England to describe what is now recognized as the usual variety of chickenpox. Since that time, only sporadic reports of true varicella bullosa with an occasional illustration have appeared in the literature. In 1866, Hebra,[4] in discussing pemphigus acutus seu febrilis, briefly described "varicella bullosa and those forms of herpes in which the vesicles frequently pass into bullae." In 1881, Kempf[5] reported a case of bullous chickenpox which he called varicella globularis. In 1885, Geddings[6] described in detail a similar case in a 5-year-old girl. In 1894, Morgan[7] gave an excellent account of the lesions of varicella bullosa, illustrating his discussion with a report on a 7-month-old male patient. Sporadic cases of varicella bullosa were reported by Stephenson,[8] Stuart,[9] Pye-Smith,[10] and Freeth,[11] and described by others.[12] It is the purpose of this report to describe three cases of varicella bullosa.

Formation of bullae is considered a rare variation or manifestation of chickenpox. This report describes three cases of varicella bullosa. All patients had the usual initial symptoms of chickenpox and all had had known contact with chickenpox. Each bulla appeared to develop from a single chickenpox vesicle of the usual configuration. The bullae appeared in crops, and scattered over the intervening skin were normal pocks in various stages of development. Constitutional symptoms were relatively mild, significant complications were absent, and the course of the disease was under two weeks. None of the patients showed bullous involvement of the mucous membranes. The authors do not agree with others who consider the disease bullous impetigo, nor do they consider it pemphigus acutus, but rather a rare manifestation of chickenpox.

Reports of Cases

Case 1.—An 11-month-old boy was admitted to the Ohio State University Health Center, Infectious Disease Service, on May 11, 1959. Two weeks prior to admission he had been exposed to an older brother with chickenpox. Four days before admission he developed a rash on the head and face in crops of macules, papules, and vesicles. Coryza developed at the same time as the skin lesions. By the next day the rash had become generalized. The parents noticed on the day before admission that the vesicles were steadily increasing in size, becoming "large blisters" that were of sufficient concern to them to seek medical attention. At this time the child developed a temperature of 103 F (39.4 C) and vomiting. Some of the bullae had ruptured, leaving excoriated surfaces. Figure 1 illustrates the bullae as well as the usual chickenpox lesions.

The history revealed that the patient had had a normal birth and development. The only previous illness was pneumonia six months prior to admission which had been treated with penicillin, followed by prompt recovery. A 2-year-old brother had chickenpox with two or three small bullae at the same time as the patient. (This observation was not confirmed by a physician.)

Physical examination revealed a well-developed, well-nourished boy who was fretful but did not appear acutely ill. Rectal temperature was 101.4 F (38.6 C), pulse rate 120 per minute, respirations 16 per minute, and weight 21.5 lb. (9.8 kg.). A generalized polymorphous eruption was seen over the body; however, the eyes, auditory canal, and mucus membranes of the mouth, nose, and throat were not involved. The rash was characterized by lesions in varying stages of development from macules, papules, and vesicles to bullae as large as 7 cm. in the long axis. Denuded crusting areas representing ruptured bullae were seen on several areas of the body. The lesions were irregular in outline, generally oblong, and situated on an erythematous base 1 to 2 cm. wide. The bullae were soft, thin-walled, sagging, filled with clear, straw-colored fluid, and ruptured easily at the upper margin. One bullous lesion was slightly hemorrhagic.

Hemogram on admission revealed 10,200 leukocytes per cubic millimeter, with a differential count of 50% neutrophils, 48% lymphocytes, and 2% mono-

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cytes; erythrocytes, 4.6 million per cubic millimeter; and hemoglobin level, 10.2 Gm.%. Urinalysis revealed no abnormalities. Cultures of fluid aspirated from several bullae showed no growth.

For three days after admission bullae continued to develop from the usual vesicular lesions of chickenpox. Many vesicles did not progress to the bullous stage. Some of the later lesions were abortive in their evolution, stopped at various stages, and crusted over. Some of the bullae ruptured, leaving a raw surface without necrosis or ulceration, while others appeared to dry up. Body temperature was not elevated beyond 102 F (38.9 C) and returned to normal after the patient had had two days of supportive therapy. The infant continued to eat well while in the hospital. At the time of discharge, six days after admission, all lesions were well on their way to healing without evidence of infection or ulceration. Epithelialization was occurring over the denuded areas.

Case 2.—A 14-month-old boy was admitted on March 11, 1955. Two weeks before admission he had been exposed to an older sister with chickenpox. Three days prior to admission a maculopapular erythematous rash had been noted on the abdomen, extremities, and genitalia which spread to the head and the remainder of the trunk within 24 hours. The lesions became vesicles typical of chickenpox, and lesions in various stages of development were seen scattered over the body. One day prior to admission some of the vesicles had progressed to form bullae. Associated with the eruption were anorexia, fever, irritability, and pruritus. Scratching of the bullous lesions resulted in rupture, leaving crusted denuded areas. Shortly before admission the child had had a generalized convulsion that lasted five minutes.

The history revealed that the patient had had a normal birth, growth, and development and had received initial diphtheria-pertussis-tetanus immunizations. Sixteen days prior to admission the patient had received one injection of penicillin for tonsillitis, with prompt improvement.

Physical examination revealed a well-developed, well-nourished child who appeared acutely ill. Rectal temperature was 104.6 F (40.3 C), pulse rate 140 per minute, respirations 30 per minute, and weight 21 lb. (9.5 kg.). There was a generalized rash involving the skin of mainly the trunk, neck, face, and thighs with a few scattered lesions on the arms and legs. The mucus membranes were not involved. The rash was characterized by lesions in various stages of development from macules, papules, and vesicles and bullous lesions which measured up to 5 cm. in diameter. The bullae were surrounded by 1 to 2 cm. of erythema. The lesions about the neck were covered with a yellowish crust.

Hemogram on admission revealed 12,150 leukocytes per cubic millimeter, with a differential count of 30% neutrophils, 57% lymphocytes, and 13% monocytes; erythrocytes, 4,600,000 per cubic millimeter; and hemoglobin level, 12.8 Gm.% Urinalysis revealed no abnormality. Chest roentgenogram revealed no abnormalities. Cultures of the denuded areas of the skin grew hemolytic Staphylococcus aureus which was coagulase-negative.

Shortly after admission a spinal tap was performed which was normal in all respects. The patient was started immediately on therapy with penicillin and streptomycin given intramuscularly, as well as neomycin given topically, because of possible bacterial infection of the lesions. After the second day no new lesions formed and crusting continued. The patient became afebrile after the third hospital day. His irritability decreased and his appetite improved. He was discharged on the sixth hospital day, with crusting lesions of various sizes without evidence of necrosis, ulceration, or infection. Epithelialization had begun in the denuded areas.

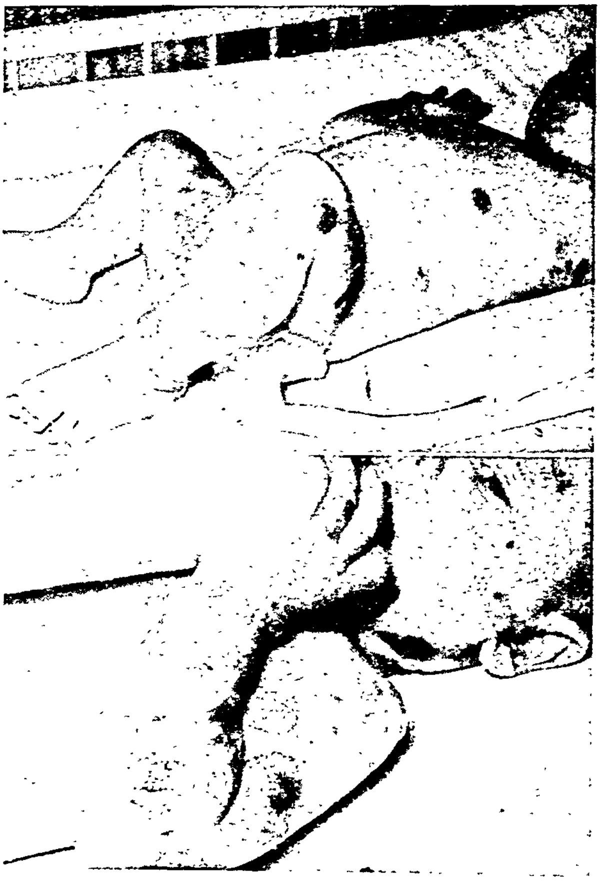

Fig. 1 (case 1).—Varicella bullosa: photograph, showing bullae and usual chickenpox lesions.

Case 3.—A 17-month-old girl was admitted to the Infectious Disease Service March 31, 1955. It was known that the child had been exposed to chickenpox three weeks previously. Five days prior to admission a typical chickenpox eruption had developed on her face which soon spread to the trunk and extremities. Lesions in various stages of development were noted. On the day of admission denuded raw areas up to 3 cm. in diameter that represented ruptured bullae were of concern to the mother, who then brought her to the hospital.

The patient's history revealed that her birth and development had been normal. She had received diphtheria-pertussis-tetanus and smallpox immunizations. Two months prior to admission she had developed fever and convulsions the causes of which were not determined.

Physical examination revealed a well-developed, well nourished female infant who was alert but appeared irritable and in moderate distress. Temperature was 104 F (40 C), pulse rate 116 per minute, respirations 22 per minute, and weight 24 lb. (10.9 kg.). There was a generalized eruption with various stages from macules, papules, and vesicles along with several bullae measuring up to 3 cm. in diameter. Where bullae had ruptured there were denuded raw areas, some of which were crusted at the edges. All the lesions were situated on an erythematous base.

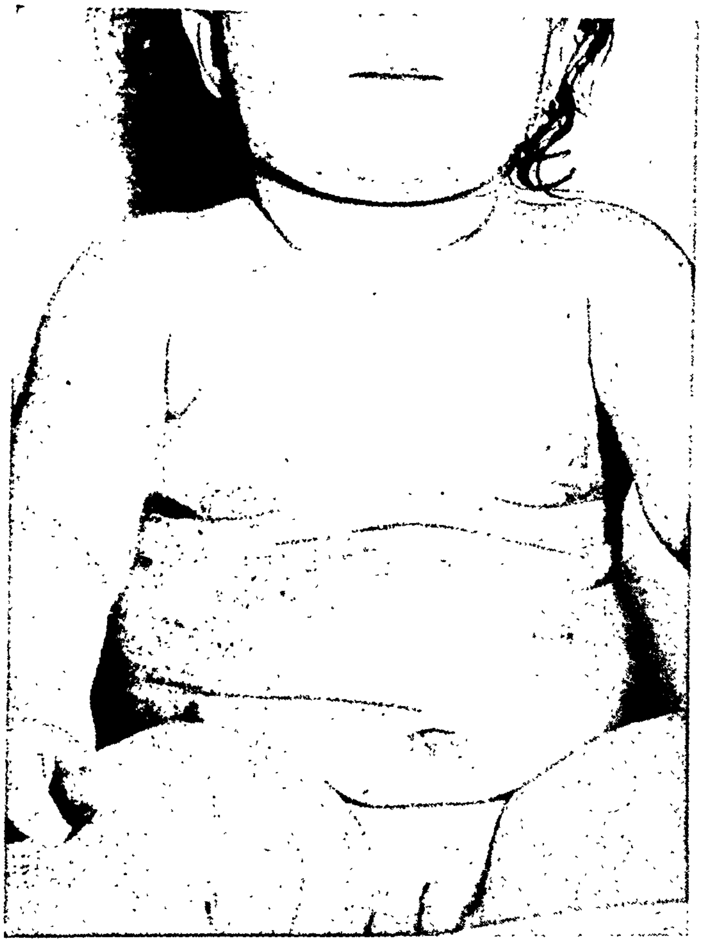

Fig. 2 (case 3).—Photograph, showing residual appearance of involved bullous areas of skin in patient with varicella bullosa.

Hemogram on admission revealed 8,900 leukocytes per cubic millimeter, with a differential count of 55% neutrophils, 42% lymphocytes, and 3% monocytes; erythrocytes, 3.7 million per cubic millimeter; and hemoglobin level, 9.1 Gm.%. Cultures of the denuded skin areas grew hemolytic Staph. aureus, but those aspirated from bullae were reported as negative. Blood culture was negative. Cultures of the throat revealed predominantly alpha hemolytic streptococci, with a few beta hemolytic streptococci.

Because of the suspected secondary bacterial infection, the patient was treated promptly with penicillin and streptomycin given intramuscularly. On the second hospital day she became afebrile, although new vesicles continued to appear and new bullae continued to develop from the vesicles already present. No new lesions formed after the third hospital day, after which the lesions healed rapidly. She was discharged on the seventh day. Figure 2 illustrates the residual appearance of the involved bullous areas of the skin.

Comment

Of three cases of varicella bullosa presented, the disease began in each patient with the usual prodromes of chickenpox, and there was a history of known contact with chickenpox. Each bulla, in our patients, appeared to develop from a single chickenpox vesicle of the usual configuration. In one patient the bullous lesion reached a diameter of 5 cm. The bullae appeared in crops, as in the usual form of chickenpox. Not all the pocks became bullae. Scattered over the intervening skin were normal pocks in various stages of evolution and involution. Each bulla was filled with a clear fluid and was surrounded by a zone of erythema 1 to 2 cm. wide. The epidermal coverings of most bullae were exceedingly thin and ruptured early, usually at their upper border, before they had had time to become distended by their fluid content. Not all the bullae became opalescent or pearly. Some rapidly dried up in the center, producing a yellowish brown crust. When the bullae ruptured or the crust separated from the underlying skin, the resulting denuded surface showed no tendency to necrosis or ulceration and healed rapidly with no more scarring than is found in the average case of chickenpox.

The constitutional symptoms were relatively mild, significant complications were absent, and the entire course was less than two weeks, as in the usual case of chickenpox. None of our three patients showed bullous involvement of mucous membranes.

In 1927, Eldridge and Rivers[13] contended that varicella bullosa should be called bullous impetigo and that it is due to a complicating bacterial infection rather than to the virus of varicella. They described a case of varicella with bullae from which hemolytic Staph. aureus was cultured. Welch and Schamberg[14] had previously arrived at this opinion and used the term "impetigo varicellosa." Ronaldson and Kelleher[15] reported a case of varicella bullosa, with associated diphtheria, in a 7-year-old girl. Cultures of the bullae were negative. Pye-Smith,[10] who observed the progression of marked vesicles into bullae, was unable to culture pathogenic organisms from the bullous lesions in one child. In two of our three cases presented above cultures from unruptured bullae were negative although Staph. aureus was cultured from the skin surface of previously ruptured bullae. It is our opinion that the formation of bullae is an unusual manifestation of the varicella itself rather than a complicating infection, although it is possible that they can become infected with pyogenic bacteria.

The lesions and course of the disease in our patients were not consistent with pemphigus acutus, in which the bullae are seated on normal skin and appear in successive crops but are bullae from the beginning. The bullae of pemphigus have a thicker epidermal covering than those of varicella bullosa, which allows the bullae to become tense before rupturing. In pemphigus acutus the constitutional febrile symptoms, as each new crop appears, are severe in contrast to the generally mild course of varicella bullosa.

Summary

Three cases of varicella bullosa, reported by us, present a rare manifestation of chickenpox. If uncomplicated by secondary infection, the course is not unlike that of the usual case of chickenpox, differing only in the size of the lesions. Photographs of the lesions illustrate their characteristics.

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FETAL ELECTROCARDIOGRAMS, SHOWING CARDIAC MALFORMATION, INCLUDING HEART BLOCK

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Antenatal electrocardiograms were made from 517 subjects. This has made possible a study of the ECG'S in those cases in which a presumptive diagnosis of congenital heart disease was made antenatally and confirmed postnatally. In three infants heart block was recognized before birth, and two of these died soon after birth; the third survived. In a fourth infant, who died five days after birth, autopsy revealed a coarctation of the aorta and so explained the abnormal ventricular complexes that had been recorded before birth. Antenatal ECG'S not only promise to give information that may help the pediatrician in preparing for postnatal difficulties but also may yield fresh clues to the origin of congenital heart disease.

Recent improvement in fetal electrocardiographic instruments, technique, and understanding make possible more than a quantitative increase in accuracy. It has been shown that a high level of accuracy in demonstrating the fetal electrocardiogram is possible in about the 22nd week of embryologic age, and again near term.[1] It has also been shown that the fetal ECG is a useful tool for the early diagnosis of multiple pregnancy.[2] With increased experience in the use of fetal electrocardiographic technique resulting from many recordings, new information has become available. In this communication, selected cases which provide antenatal demonstration of complete heart block and other instances of congenital malformation will be reported from the above material. One instance is included which showed an abnormal fetal QRS

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CLINICAL NOTES

AMPHOTERICIN B IN BILATERAL CAVITARY HISTOPLASMOSIS

REPORT OF A CASE WITH TWO-YEAR FOLLOW-UP

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Most cases of pulmonary histoplasmosis seem to have an acute but benign course, and the infection usually subsides without the necessity of specific therapy. Many acute pulmonic Histoplasma infections are probably never specifically recognized.

The chronic pulmonary form of the disease has received much recognition during recent years.[1] It has been shown that the clinical and roentgenographic findings may closely simulate pulmonary tuberculosis.[2] Furcolow and Brasher[3] found a surprising incidence of patients with unrecognized chronic pulmonary histoplasmosis languishing in tuberculosis sanitoriums throughout the central part of the United States. Unfortunately, once cavitation has occurred in histoplasmosis the natural clinical course is slow dissemination of the infection and deterioration of the patient's condition until he dies.[4]

Until the development of amphotericin B there was no specific therapy of value for these patients. Amphotericin B is an antifungal antibiotic isolated from the species of Streptomyces, which has been found to be effective in the cure of both hamsters and human beings suffering from Histoplasma infection.[5]

In 1957, after a course of amphotericin B was administered to a woman severely ill with multiple bilateral apical cavitary disease, a dramatic cure of her infection occurred. The patient was 45 years of age when first seen in June, 1957, had borne two children and enjoyed good health until January, 1956. For 10 years she had worked as a cashier in a local restaurant. There was no history of exposure to barns or chicken houses. She smoked one package of cigarettes daily. In January, 1956, she developed a febrile illness and cough. The fever abated gradually but the cough persisted, with production of mucoid sputum. The appearance of hemoptysis caused her to seek medical consultation. Because of findings on roentgenograms of the chest in March, 1956, she was admitted to Boehne Tuberculosis Sanitarium where repeated studies of sputum and gastric washings failed to show acid-fast bacilli. One fungus culture showed Histoplasma capsulatum. Three months of rest in bed brought no improvement in her condition as revealed by roentgenograms of the chest, but the patient gained some weight, felt stronger, and left the hospital in June, 1956. By September, 1956, she had again lost weight and was unable to work. For one week she was a patient in a general hospital, where slight fever, leukocytosis, and an elevated sedimentation rate were noted. The roentgenogram of the chest showed bilateral upper lobe disease with diffuse infiltration and cavitation (fig. 1).

By June, 1957, her health had deteriorated and she was again hospitalized. Her daily afternoon temperature rose from 100.0 to 101.0 F (37.8 to 38.3 C) and her cough produced about 30 to 50 cc. of mucoid sputum daily. Loss of weight had continued to virtual cachetic proportions. No mucocutaneous lesions were found. There was noticeable increase in the anteroposterior diameter of the chest, and the diaphragms were low and moved poorly during respiration. Percussion note was hyperresonant in all areas, and the breath sounds were distant without rales or friction rub. There was no enlargement of lymph nodes, liver, or spleen. The hemoglobin level was 9.6 Gm. per 100 cc., with a hematocrit value of 32%. The white blood cell count was 8,950 per cubic millimeter with monocytes 6%, lymphocytes 22%, stab forms 2%, neutrophils 60%, basophils 2%, and eosinophils 8%. Result of the Mazzini test for syphilis was negative. The fasting blood sugar level was 96 mg.%, and the nonprotein nitrogen level was 25 mg.%. The sedimentation rate was 58 mm. in one hour, the cephalin flocculation was 4 + in 48 hours, the serum albumin level was 3.1 Gm.% and the globulin level was 3.2 Gm.%. The roentgenogram of the chest showed an increase in the upper lobe infiltration and a great increase in the size of the cavities (fig. 2). Result of testing of skin to first and second strength purified protein derivative (P. P. D.) gave negative results. Result of the histoplasmin skin test was strongly positive. Sputum cultures showed unidentified yeast. A biopsy specimen of a scalene node was normal.

The patient received a transfusion of 1,000 cc. of whole blood. She was given vitamins, but she would eat sparingly of her high protein diet. A 10-day therapeutic trial with administration of streptomycin and isoniazid brought no change in the clinical picture. Nystatin, given orally, 4 Gm. daily, produced a transitory disappearance of fever for three days but no evidence of clinical improvement in the patient after 14 days.

In the laboratory of the United States Public Health Service Histoplasma capsulatum was demonstrated in three consecutive daily sputum specimens, and histoplasmosis complement fixation was positive in a dilution of 1:256.

On Aug. 16, 1957, the patient received her first intravenously given dose of amphotericin B, and from then until Dec. 14, 1957, she received about 90 intravenous injections of 50 mg. each. Initially, there were febrile reactions to the drug, but these were controlled with administration of tripelennamine and salicylate; after two weeks the latter drugs were no longer necessary. In September and October, the patient had diarrhea without demonstration of staphylococci or other pathogens in the stool. The diarrhea was controlled with small doses of paregoric and kaolin therapy. Local venous thromboses were a problem, but the clinical response of the patient was dramatic. After the first three days of amphotericin B therapy, her fever ceased and never returned. During these months she gained 28 lb. (12.7 kg.), cough and sputum diminished to an irreducible minimum of 15 cc. daily, and the hemoglobin and serum albumin levels spontaneously returned to normal. The white blood cell and differential counts were remarkable only for a slight persistent eosinophilia. Periodic testing failed to show any evidence of renal or hepatic toxicity.

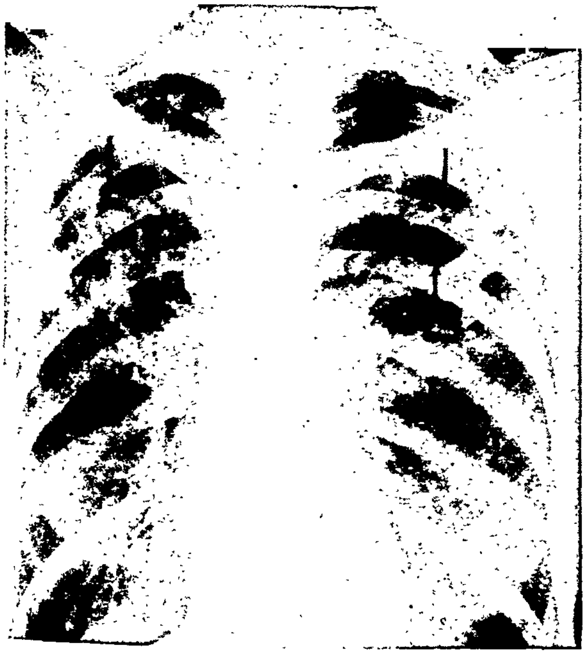

Fig. 1.—Roentgenogram showing bilateral upper lobe cavitation present *nine months after onset of illness.*

The roentgenogram of the chest made in December, 1957, showed some decrease in the size of the pulmonary cavities and considerable decrease in the surrounding infiltration. The lateral view of the chest showed increased anteroposterior diameter and typical findings of emphysema (fig. 3 and 4).

Since December, 1957, the patient has been observed closely and examined in the office at least once a month. Cough with small amounts of mucoid sputum, periodically blood streaked, continues with occasional exacerbation associated with winter-time respiratory infection. Two-week trials of therapy with sulfonamide or tetracycline have effected little change in the cough and sputum. There has been a slow definite increase in exertional dyspnea associated with evidence of slowly increasing pulmonary emphysema but no clinical evidence of pulmonary hypertension. In addition to her pulmonary disease the patient has difficult socioeconomic circumstances.

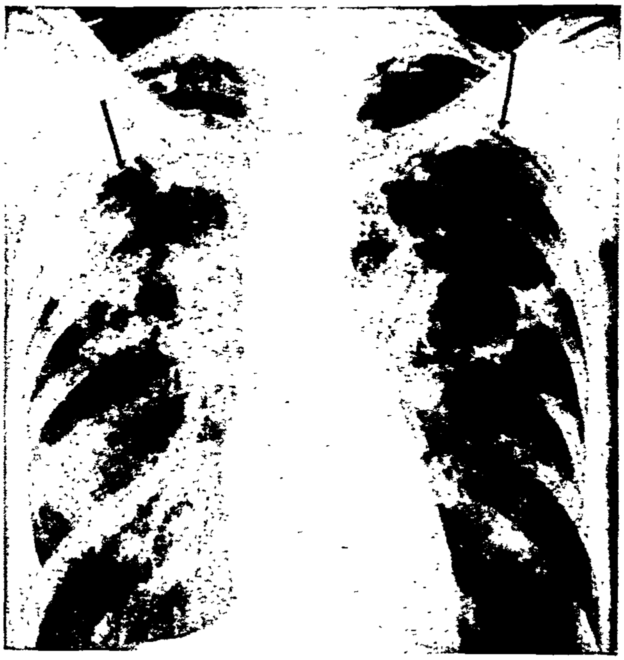

Fig. 2.—Roentgenogram showing larger thin-walled upper lobe cavities with moderate evidence of inflammatory infiltration.

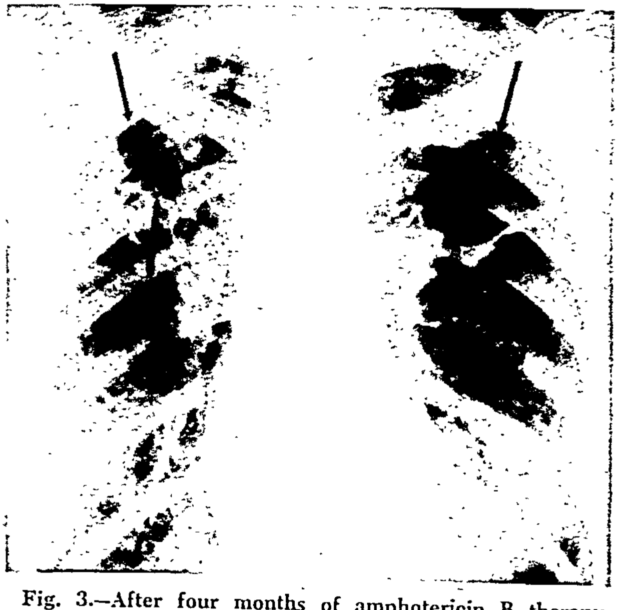

Fig. 3.—After four months of amphotericin B therapy, cavities are slightly decreased in size, and inflammatory infiltration has receded.

From the time of initiation of amphotericin B therapy, surgical therapy to remove or close the pulmonary cavities has been considered. However, any attempt at lobectomy has been rejected because (1) the pulmonary cavities have been virtually asymptomatic; (2) complete removal of the cavities would involve bilateral procedures; (3) the lower lobes are severely emphysematous, and resection of the upper lobes would entail a considerable risk; and (4) the patient's chief difficulty for the past two years has been her emphysema and pulmonary insufficiency, for which any surgical procedure would seem of no avail.

It is noteworthy that there has never been any suggestion or evidence of recurrence of active histoplasmosis infection. The old areas of cavitation and infiltration seem to be slowly improving, as revealed by chest x-ray (fig. 5).

Six consecutive daily sputum specimens sent to the United States Public Health Service laboratory failed to show Histoplasma organisms. Her general health is much better than it was two years previously at the time of initiation of amphotericin B therapy. She is able to provide a home for her two teen-age sons.

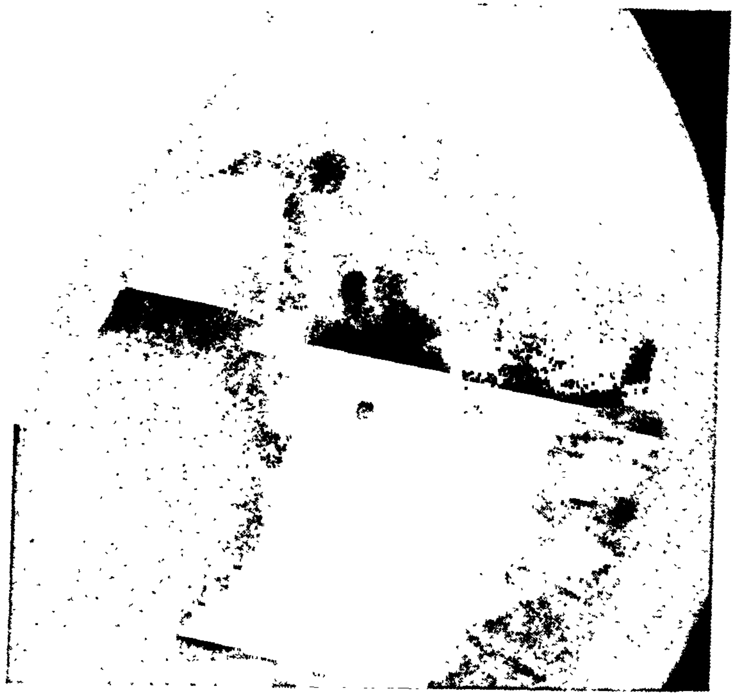

Fig. 4.—Lateral view of chest showing thoracic kyphosis and typical changes of emphysema.

Summary and Conclusions

In a case of chronic bilateral cavitary histoplasmosis, administration of amphotericin B was associated with a dramatic improvement in the patient's health. This case demonstrated that pulmonary histoplasmosis, although usually a benign disease, can in every way mimic pulmonary tuberculosis and pursue a relentlessly progressive course. Since effective chemotherapy now exists for both histoplasmosis and tuberculosis, precise differentiation of the two is imperative. This case demonstrates also the tendency for histoplasmosis to heal with pulmonary fibrosis, bronchial distortion, and emphysema. Perhaps earlier initiation of specific therapy would prevent these late sequelae.

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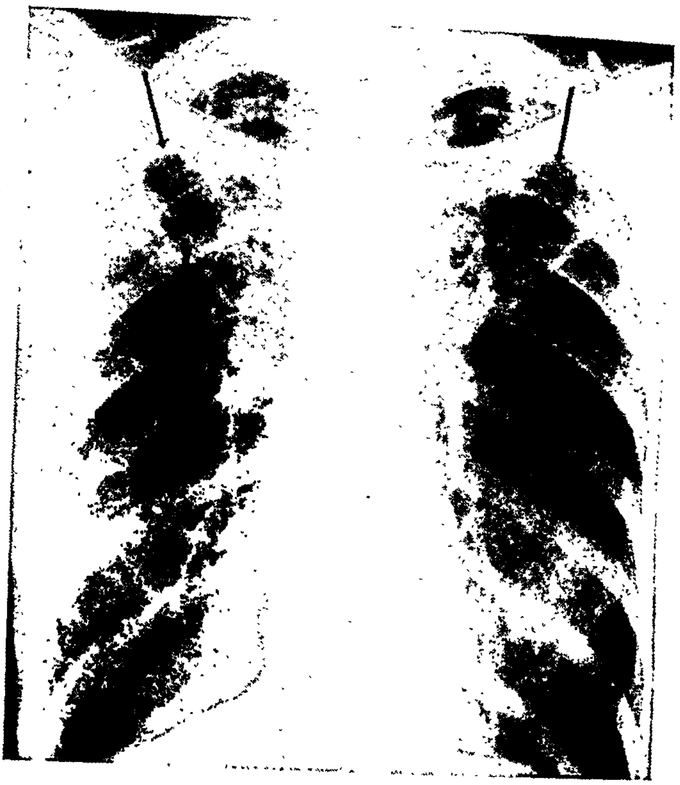

Fig. 5.—Eighteen months after completion of amphotericin B therapy, cavities and infiltrations show further decrease; hila seem higher.

The amphotericin B used in this study was provided by Dr. Michael Furcolow, who also gave helpful advice and encouragement during the treatment period.

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DUPLICATION OF THE RECTUM CONTAINING GASTRIC MUCOSA

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and
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Duplications may occur in any portion of the alimentary tract from the base of the tongue to the anus. These may be elongated, tubular structures duplicating large or small portions of the alimentary canal. They are seen also as cystic structures intimately attached to the alimentary system. Finally, they may take the form of giant diverticula with free connection to some part of the bowel. However, the inclusive term "duplication of the alimentary tract" is applied to all these anomalies. Furthermore, a true duplication must contain a coat of smooth muscle, connect with some portion of the alimentary canal, and be lined with alimentary tract mucous membrane.[1] This condition should not be confused with Meckel's diverticulum, which is an entirely different entity with a distinct embryonic derivation.

The relatively small number of duplications reported in the literature would suggest that this represents an uncommon condition.[2] Duplications are seen most often in the small intestine and are of extremely rare occurrence in connection with the rectum. Dohn and Povlsen,[3] reviewing the literature in 1956, found but 315 cases of duplication reported. Of these, 10 (3.2%) were connected with the rectum.

From an embryologic standpoint, the origin of duplications remains obscure. Several theories have been advanced,[4] none of which has been universally accepted.

Gastric mucosa frequently is found as the lining membrane in alimentary tract duplications, but this is usually observed in connection with the small intestine. Our review of the literature failed to reveal a single case of duplication connecting with the rectum that contained gastric mucosa.

The following is a case report of a duplication of the rectum in the form of a giant diverticulum which contained gastric mucosa with ulceration. This was, in effect, a peptic ulcer of the rectum.

Report of a Case

The patient was a well-nourished 4-year-old girl, who was seen for the first time in our office. The sole complaint was rectal bleeding. For the preceding two years the mother had noted the frequent appearance of blood in the stool. This was bright red and usually scant, but on several occasions fairly large quantities were passed. The blood most often was streaked on the surface of the stool or free but at times was seen to be somewhat mixed with the stool. Blood-stained underclothing was frequently observed. The child at no time complained of any pain or discomfort. From birth, except for the bleeding described, her bowel habits were considered normal. Otherwise, the bowel history was not unusual in any respect. Likewise, the family history and complete systemic inquiry were consistent with that of a normal, healthy, intelligent child of her age.

Proctoscopic examination visualized what appeared to be a large diverticulum connecting with the lower, right, anterior rectum. The opening of this structure was surrounded by a slightly elevated cuff somewhat granular in appearance, which was located 5 cm. above the anorectal junction. On gentle air insufflation the mouth of the diverticulum could be made to open, thus exposing about 2 cm. of the interior of the pouchlike structure (fig. 1). Bright blood was seen to issue from the mouth of the diverticulum. Although the duplication was not initially palpated on digital examination, with knowledge of its presence, under gentle pressure,

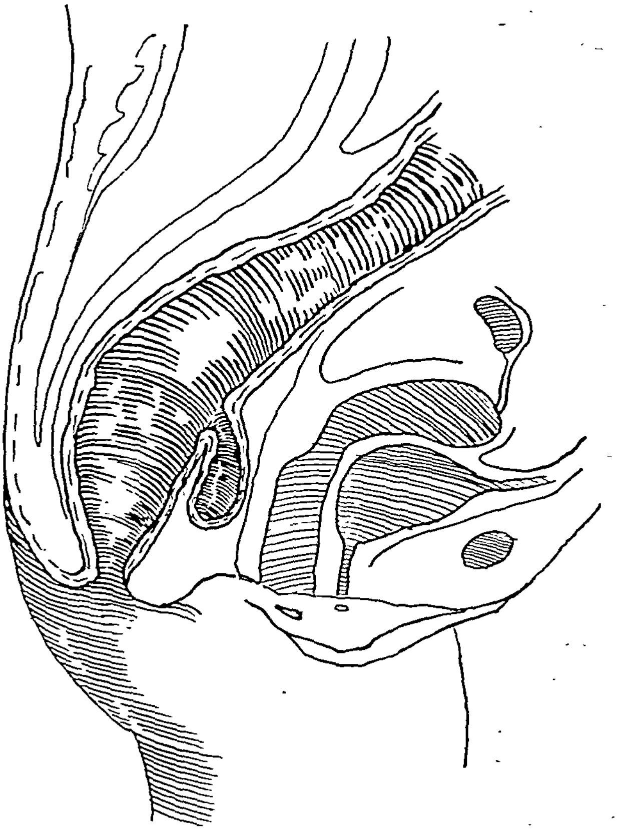

Fig. 1.—*Sketch, showing location and general proportions of duplication of rectum containing gastric mucosa.*

the finger could be made to penetrate the diverticulum for a depth of 3 to 4 cm. Otherwise, the bowel appeared normal for a distance of 23 cm.

The patient entered the East Tennessee Baptist Hospital on May 14, 1959. Her general physical examination and laboratory findings were not remarkable. Barium enema studies did not satisfactorily visualize the duplication but otherwise demonstrated what appeared to be a normal gastrointestinal tract.

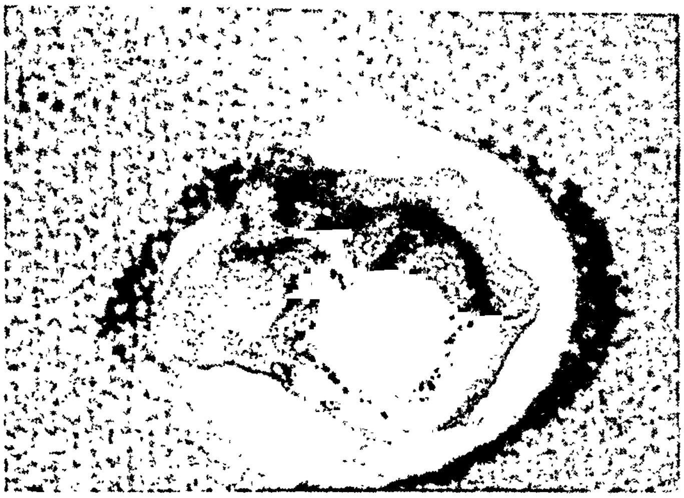

Fig. 2.—Photograph of gross specimen, showing appearance of diverticulum from bowel surface.

An operation was performed on May 16, 1959. Under general anesthesia, with the patient in the jack-knife position, a triangular incision was started on the right anterior quadrant of the perianal skin at a point directly opposite the diverticulum. This was extended from the apex on the skin to include the diverticulum. The triangular flap thus outlined was freed from the underlying structures to include the entire duplication. This was accomplished easily by inserting the finger in the diverticulum and elevating it in this manner. The dissection was simple, since the diverticulum was not adherent to the underlying tissues. The duplication had the general proportions of the finger of an average-sized glove but with about half the depth which, in the fresh specimen, measured 3 cm. in depth and 2 cm. in diameter (fig. 2). When the diverticulum was freed, the flap was excised above this. The cut portion of the bowel wall was further mobilized and then advanced down over the denuded area and fixed to the internal border of the external sphincter with interrupted 00 plain catgut sutures. Bleeding points were ligated, and the external aspect of the wound was allowed to remain open. The specimen was examined, and the microscopic description is as follows: In the sections taken from the mucosa deep in the diverticulum, cells resembling both chief and parietal cells are arranged in the histological pattern of gastric mucosa. These are covered by mucous-secreting, nonspecific intestinal cells. This change

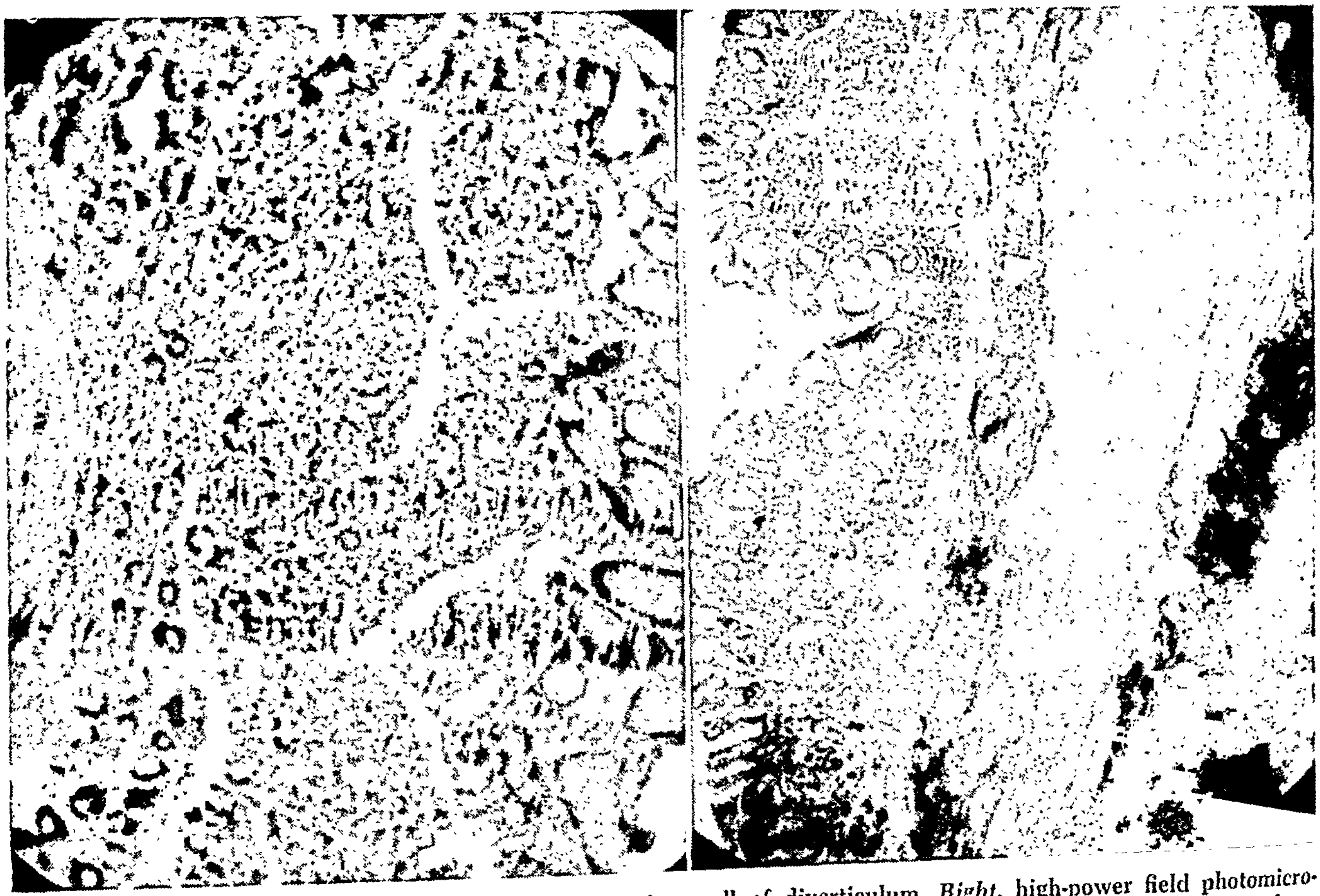

Fig. 3.—*Left*, low-power field photomicrograph, showing wall of diverticulum. *Right*, high-power field photomicrograph, showing mucous membrane lining of duplication: note parietal and chief cells in typical gastric mucosal arrangement.

blends into typical colonic mucosa at either end of the mouth of the diverticulum. The anal skin is normal. The chief and parietal cells lie on a fibrovascular membrane which contains thin but definite muscle.

The pathological diagnosis was diverticulum of rectum containing gastric mucosa (fig. 3). The patient was discharged from the hospital the second day after operation. Her postoperative course was uneventful, the child engaging in normal activity throughout. Healing was complete in three weeks and the patient has remained well up to the time of writing.

Summary

In a case of duplication of the rectum which contained gastric mucous membrane, an operation to correct the condition proved successful. A search of the literature did not reveal a report of a similar case.

115 Blount Ave. (20) (Dr. Stockman).

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PERICARDITIS AFTER ACUTE MYOCARDIAL INFARCTION

RELAPSES OVER PERIOD OF TWENTY-EIGHT MONTHS

William Dressler, M.D., New York
and
Samuel S. Leavitt, M.D., Palos Heights, Ill.

Pericarditis may accompany acute myocardial infarction as an insignificant feature or as a major complication which is often associated with pleurisy and not infrequently with pneumonia. The triad, resembling closely the postcardiotomy syndrome, has been referred to as post-myocardial-infarction syndrome.[1] One of its characteristic features is a tendency to relapse. The following case is reported because a post-myocardial-infarction syndrome continued to recur over a period of 28 months.

Report of a Case

A 44-year-old man fell ill on Oct. 28, 1956, and had a sensation of severe pressure in the precordial area radiating to the left shoulder and arm. He was hospitalized on the same day, and an electrocardiogram showed features indicative of a recent anteroseptal-wall myocardial infarction. The patient felt better for four days, but on the fifth day he experienced gripping chest pain which was aggravated by supine position and deep inspiration. A pericardial friction rub was heard for three days. Then pain and rub subsided and the patient progressed well. He was treated with anticoagulants, and this therapy was continued after the patient was discharged from the hospital, on Dec. 10.

On Dec. 13 the patient was readmitted because he was seized again with a feeling of severe pressure in the precordial area which did not radiate to the arms. The distress was aggravated by breathing and supine position. It was severe enough to require frequent injections of meperidine (Demerol) hydrochloride for partial relief. The electrocardiogram showed no signs of extension of the myocardial infarction. A pleural friction rub was audible at the base of the left lung. Roentgenograms of the chest which were made prior to the end of the first hospitalization on Dec. 7 showed clear lung fields and a heart of normal size (fig. 1*A*). A repeat study on Dec. 14 revealed that the cardiac silhouette was enlarged, its waist was widened, and the normal segmentation of the left contour was obscured (fig. 1*B*). There was evidence of pleural effusion on the left side and pulmonary infiltration at the right base. On Dec. 17 regressive changes were noted (fig. 1*C*). The cardiac silhouette, notably its waist, were smaller, and segmentation of the left contour was again recognizable. Pleural effusion and pulmonary infiltration were obviously disappearing. Clinical improvement was rapid and the patient was discharged on Dec. 21.

A third admission because of chest pain of a pleuropericardial type occurred on Jan. 8, 1957. Roentgenograms revealed enlargement of the heart silhouette and an infiltration in the mediobasal segment of the left lower lobe. Chloramphenicol (Chloromycetin) was administered. At no time was there bloody expectoration. It was thought that the relapses were due to pulmonary embolisms. Improvement was rapid, and the patient was discharged on Jan. 17.

In February, 1957, the patient went to Florida, where he suffered a relapse that showed all the

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characteristics of the previous attacks and which subsided after a few days. A fifth attack occurred in May, 1957, which necessitated readmission to the hospital. An x-ray film of the chest which was taken on May 27 (fig. 2*A*) revealed a somewhat enlarged heart silhouette of globular shape and normal pulmonary findings. On May 31 (fig. 2*B*) the heart silhouette appeared normal again. Pulmonary embolism seemed the most likely cause of the relapse. Later on, however, it was recognized that the clinical features fitted the description of the post-myocardial-infarction syndrome.

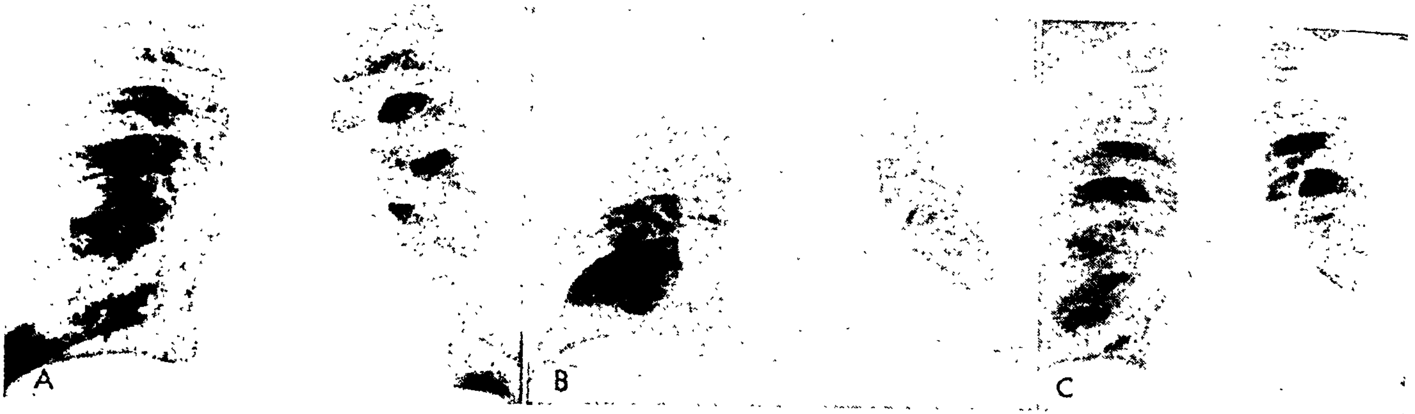

Fig. 1.—Roentgenograms of heart. *A*, heart is of normal size. *B*, cardiac silhouette is enlarged, its waist is widened, and normal segmentation of left contour is obscured. There is evidence of pleural effusion on left side and pulmonary infiltration at right base. *C*, cardiac silhouette is smaller and its waist narrower. Pulmonary infiltration and pleural effusion are regressive.

In November, 1957, the patient went to the Mayo Clinic for an examination and suffered there another attack of pleuropericardial pain. There was roentgenographic evidence of a small pleural effusion at the left side. The patient's history and previous x-ray films which were available supported a diagnosis of postinfarction pleuropericarditis. The patient was advised to discontinue anticlotting therapy and to take steroids if he suffered another relapse.

Two more attacks of the same type followed, one in October, 1958, and another in March, 1959. During the last attack transient enlargement of the heart silhouette was again observed. Administration of small amounts of steroids seemed to hasten recovery, and the patient was able to remain in domestic care. After five days administration of the steroids was discontinued with no ill effect. No relapse has been observed since that time.

Comment

The patient whose case history is reported here suffered, after acute myocardial infarction, eight attacks of pericarditis which were often associated with pleuritis and sometimes with pneumonitis. Apart from the frequent and painful relapses the complication appeared to be quite benign. Each episode was self-limited and lasted only for a few days. In the intervals between attacks, which grew longer in the course of the disease, the patient was free of complaints and enjoyed such activities as playing golf. The last attack was particularly short, probably due to the administration of adrenal steroids. It is of interest that discontinuance of this therapy was not followed by a relapse.

A case of postmyocardial infarction syndrome was previously reported in which the manifestations of the syndrome were suppressed for more than two years by continuous use of steroids.[2] Whenever the steroids were discontinued, a severe relapse and development of pericardial and pleural effusion and pneumonitis invariably resulted. In the present case, however, each attack healed spontaneously after lasting from five to eight days. The total duration of the illness was 28 months.

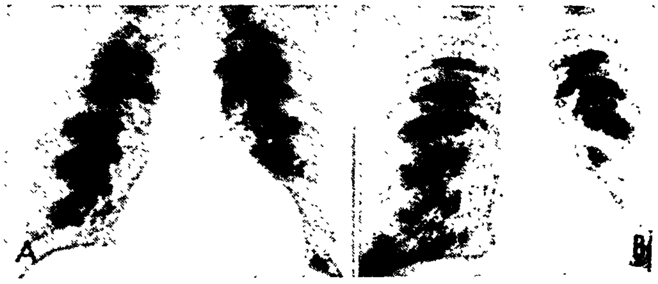

Fig. 2.—*A*, heart silhouette somewhat enlarged and globular in shape. *B*, heart silhouette after it returned to normal size.

Summary

A patient suffered relapses of the post-myocardial-infarction syndrome seven times over a period of 28 months.

1150 Fifth Avenue (Dr. Dressler).

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COMMITTEE ON COSMETICS

Report to the Committee

The Committee on Cosmetics has authorized publication of the following report.
VERONICA LUCEY CONLEY, *Ph.D., Secretary*

PHYSIOLOGICAL AND PATHOLOGICAL CHANGES IN SKIN FROM SUNBURN AND SUNTAN

Allan L. Lorincz, M.D., Chicago

The total solar radiant energy which reaches the earth's surface at normal incidence amounts to about 80 million ergs per square centimeter per minute under optimal conditions. Only about 0.2% of this energy lies within the invisible ultraviolet range of wavelengths which can elicit redness or sunburn in human skin. An exposure to about 3 million ergs per square centimeter of these sunburn-producing wavelengths is required to produce a mild erythema in untanned normal white skin. Therefore, an exposure time of about 20 minutes to direct summer midday sunshine can result in sunburned redness in such skin. Tenfold extension of this exposure time results in a painful blistering sunburn.

Factors Influencing Production of Sunburn and Suntan

The action spectrum for sunburn production by ultraviolet radiation is shown in the figure. The shaded area on this figure represents the short-wavelength end of the spectral distribution of solar energy at the earth's surface under optimal conditions.[1] Wavelengths below 2,900 A are not present in sunshine because of the complete filtering action of the atmosphere for these shorter wavelengths. Thus, the development of sunburn depends on the shortest tail portion of the sunshine spectrum which crosses the ultraviolet erythema-action spectrum. Numerous factors such as latitude, time of day, time of year, elevation above sea level, atmospheric turbidity, the amount of ozone in the upper atmosphere, and the reflectance of the environment enormously influence the amount of sunburn-producing wavelengths of sunshine which impinge on the skin.[2] It is further well known that the visible intensity of sunshine is by no means a reliable guide to its content of invisible sunburning radiation.

Physiological Mechanism of Sunburn

The erythema-producing wavelengths of sunlight are essentially entirely absorbed in the outer, richly cellular, avascular epidermis which is approximately 0.1 mm. thick.[1] It is clear then that the physiological and pathological changes which so prominently involve the subepidermal tissues in persons with sunburn must arise secondarily in response to the action of some substance or substances elaborated in the irradiated epidermis and diffused into the underlying dermis. The primary photochemical changes produced in the epidermis by sunburning ultraviolet irradiation have not yet been identified. Current hypotheses, however, tend toward the view that the primary photochemical metabolites are probably ultraviolet-altered proteins.[3] It has been clearly established that histamine cannot be implicated in the elicitation of an erythema produced by sunlight.[4]

Period of Latency.—After a sufficient exposure to sunlight, there is a characteristic latent period of usually not less than two or three hours before erythema appears.[5] The maximum intensity of the redness is usually reached in 10 to 24 hours, and thereafter it gradually subsides within the next one to seven days, depending on the intensity of the reaction.

The latent period preceding sunburn is strongly temperature dependent, since it has a temperature coefficient (Q_{10}) of 2.3.[6] This fact most likely means that the primary photochemical metabolite produced in the epidermis is not the direct cause of the erythema, because direct photochemical reactions have much lower temperature coefficients. It would appear that the primary photochemical product or products set off secondary, highly temperature-dependent reactions leading to the formation of the vasodilator material. The further fact that relative anoxia, induced by vascular occlusion during the period of irradiation, fails to alter the subsequent development of erythema probably means that the primary photochemical process is

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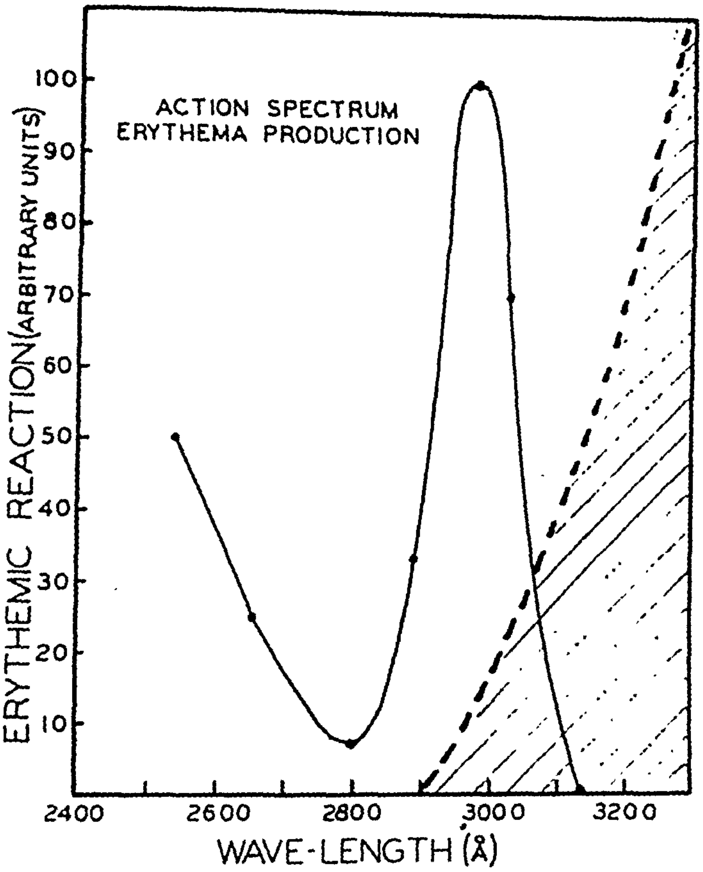
Presented at the Fifth Symposium of the Committee on Cosmetics at the Clinical Meeting of the American Medical Association, Dallas, Texas, Dec. 2, 1959.

not simply an oxygen-requiring photo-oxidative one, as is the case in some biological effects produced by ultraviolet irradiation.[7] Rather, it has been postulated that, in the chain of reaction involved in sunburning, primarily formed, short-lived, photochemical, protein-bound free radicals might give rise to longer persisting, biologically active mediators such as organic peroxides.[8]

Presenting Symptoms.—If the patient's solar exposure is excessive, in addition to the erythema, edema and blistering of the skin may develop. If extensive sunburn is this severe, systemic manifestations of chills, fever, and prostration may occur. Hyperesthesia, pain and/or itching generally appear coincident with the erythema of sunburn and usually precede blistering should it develop. An increase in melanin pigmentation and desquamation (peeling) may follow even a relatively mild erythema. The peeling may appear as late as one to two weeks after exposure.



Action spectrum for production of erythema by ultraviolet radiation (according to Blum[2]).

Systemic Effects.—Histopathologically, coincident with the development of erythema, dilated small blood vessels appear in the upper dermis, and leukocytic infiltration begins to appear there.[9] After 24 to 48 hours, alterations appear in the epidermis, which consist of cellular degenerative changes and intracellular and intercellular edema in the upper portions of the prickle cell layer. The basal cell layer of the epidermis, in general, remains remarkably unaffected. After five to seven days, the damaged superficial epidermal layer undergoes condensation. At this time, there is usually also some degree of acanthosis or thickening of the prickle cell layer and accompanying hyperkeratinization or thickening of the stratum corneum.

The vascular effects of even a single moderate sunburn induced by ultraviolet irradiation are by no means entirely over after subsidence of the erythema. For example, it has been found that the patient's whealing response to histamine is reduced for 6 to 8 months after such erythema and that impaired vasomotor tone, as measured by responses to heat and cold, is present even 15 months after such sunburn.[10] The well-known dermal basophilic degeneration, premature aging, and epidermal premalignant and malignant changes brought about by chronic solar exposure further attest to the long-lasting character of some of the alterations produced in the skin by exposure to sunlight.

In erythema due to sunburn, the usual cutaneous paling in response to the administration of epinephrine fails to occur, apparently because the reddening of the skin is based primarily on dilatation of smaller vessels rather than on primary arteriolar dilatation, with secondary passive dilatation of the smaller vessels.[11] However, hydrocortisone and analogous steroids, given locally or systemically, have suppressed or delayed sunburn in some cases.[12] In the treatment of severe sunburn, such anti-inflammatory steroids have occasionally been useful.

Suntanning Phenomenon

The darkening or tanning of the skin which follows sunlight irradiation or sunburn is a complex phenomenon. Before I describe the various mechanisms involved in suntanning, I want to review very briefly a few basic points about cutaneous melanin pigmentation.

Cutaneous Melanin Pigmentation.—Brown melanin pigment arises in specialized dendritic cells called melanocytes. In embryonic life, these cells arise in the neural crest and migrate through the developing dermis to their final locations in the skin. They can be found scattered as a network in the basal layer of the epidermis. Cytoplasmic granules in these cells bear a copper-containing enzyme, tyrosinase, which brings about the oxidation of the amino acid, tyrosine, to melanin pigment through a now familiar sequence of reactions, first elucidated by Raper and his associates.[13] During its formation, the final melanin pigment polymer becomes firmly bound to the proteins of the melanin granules. Normally, the enzyme tyrosinase is believed to be kept in a state of partial inhibition, which can apparently be released by a variety of pigmentogenic factors including ultraviolet irradiation. Melanin pigment granules can apparently be transferred via the dendritic processes of the melanocytes into epidermal cells. They accumulate especially in the basal cells in the form of supranuclear clusters or so-called caps. These supranuclear caps of melanin pigment may partly account for the resistance of the basal layer to solar damage. Melanin can protect against ultraviolet effects not only by its ultraviolet screening action but also, chemically, by acting as a repository or trap for photoactively produced electrons or reactive radicals,[1] because melanin itself has stable-free radical properties.[14] Melanin pigment is gradually swept up from the epidermis to the surface of the skin and is shed from it in the more or less continuous physiological current of epidermal regenerative proliferation, keratinization and desquamation.

Immediate Tanning Effect.—In suntanning, an initial darkening of the skin often appears a few minutes after exposure and reaches a maximum in less than one hour. This immediate tanning is brought about by the long-wavelength ultraviolet spectrum extending between 3,000 and 4,300 A, with a broad maximum at about 3,400 A.[15] The phenomenon is believed to result from the direct photo-oxidation of relatively pale tan, preformed, reduced melanin to darker, oxidized melanin. If the oxygen supply is reduced during irradiation such as by blanching the skin with pressure from a quartz plate, this immediate tanning effect can be prevented.[16] Once this type of darkening has developed, it may persist for widely varying periods, ranging from an hour or so up to more than a year.[5]

Delayed Tanning Effect.—A second type of phenomenon affecting pigmentation occurs several days after solar exposure and consists of an upward migration of melanin granules in the epidermis, probably as a result of their dispersion and retention in the dendrites of the melanocytes.[17] This type of retention and dispersion of melanin in dendritic processes of melanocytes is also seen in many inflammatory skin disorders in which epidermal cells have been mildly injured.

True Tanning Effect.—Finally, a third and most important factor in the suntanning process is the stimulation of new formation of melanin in the skin. This new formation of melanin, or true tanning, is brought about by the same ultraviolet spectrum which causes sunburn, and it begins about two days after exposure to an erythema-producing dose of such rays.[18] It reaches a maximum after about two or three weeks and begins to decline after one month. After 10 months, this tanning is usually completely gone. A number of mechanisms have been suggested to account for the increased melanin formation after erythemogenic ultraviolet irradiation, and possibly all play roles in the process.[19] These are (1) a reduction in tyrosinase-inhibitory epidermal sulfhydryl groups from such radiation; (2) ultraviolet catalysis of tyrosine oxidation to dopa (dihydroxyphenylalanine), with the small amounts of dopa thus formed serving to enhance the tyrosine-tyrosinase reaction; (3) alteration of the redox potential of the skin by the radiation so as to favor dark melanin formation; and (4) the increased skin temperature accompanying the ultraviolet erythema, which may accelerate the tyrosine-tyrosinase reaction.

Factors Which Retard or Enhance Suntanning.—A point of interest is that window glass as well as many sunscreening preparations such as those based on para-aminobenzoic acid effectively filter out the erythema-producing wavelengths of sunlight yet permit passage of longer pigment-darkening rays above 3,200 A.[20] Sunlight-induced darkening of freckles, therefore, is not prevented by such screening agents.

Endocrine and other factors which generally promote melanization also tend to enhance suntanning. For example, exposure to sunlight enhances Addisonian melanosis and the facial pigmentation of chloasma which may accompany pregnancy. A further noteworthy phenomenon, which occasionally occurs in castrated persons, is the development of tanning in areas which were sunburned even several months previously when androgenic or estrogenic steroids are administered.[21]

It is, of course, common knowledge that there are great individual variations in susceptibility to sunburning and suntanning. Fair-skinned blonds and those with reddish-blond hair in particular are especially susceptible to ultraviolet burning and show little tendency to tan except perhaps to form freckles. Susceptibility to sunburning can be expressed semiquantitatively by measuring threshold erythema-producing doses on areas of skin which are usually unexposed to the sun.

The remarkable acquired tolerance to sunshine which develops subsequent to repeated exposures has two main mechanisms, namely, increased melanin pigmentation [22] and thickening of the horny layer.[23] Both of these factors serve as highly effective screens against further penetration and damage by sunburning ultraviolet rays. That pigmentation is not the sole factor in this development of tolerance is indicated by the fact that it also occurs in completely nonmelanized skin such as is found in patches of vitiligo. Also, the thick horny layer normally present on the palms and soles, even in the absence of pigment, makes it practically impossible to sunburn these areas. The role of the stratum corneum in solar tolerance is still further pointed up by the observation that stripping the horny layers from the epidermis by repeated applications of adhesive tape lowers the threshold for sunburn.[24] Sweat also affords some protection to the skin against sunburn because it contains substances which, to some degree, can absorb ultraviolet radiation of wavelengths shorter than 3,300 A.[25]

The fact that susceptibility to sunburn-produced erythema and to the chronic cutaneous-damaging effects of sunlight need not be correlated is illustrated by the occurrence of the rare, recessively inherited familial disease, xeroderma pigmentosum. In this disorder, there is no enhanced susceptibility to sunburn, yet the skin, after only a few exposures to sunlight, develops, with remarkable ease, the degenerative, preneoplastic, and neoplastic changes which characterize chronic cutaneous solar injury.[26] Persons afflicted with this terrible disease usually succumb (before reaching adulthood) to malignant neoplasms arising multicentrically in sun-exposed skin areas.

Other Systemic Effects

The prime medically accepted beneficial systemic effect of solar exposure for man is the resulting production of vitamin D. In man, this synthesis takes place in the living epidermis which is rich in 7-dehydrocholesterol, a substance readily converted to vitamin D by irradiation with the erythemogenic wavelengths of sunlight.[27]

Systemic circulatory changes may occur after ultraviolet irradiation of the whole body surface.[28] Prominent among these changes is a reduction of both systolic and diastolic blood pressure. This reduction commences long before the sunburn reaction develops and may even be noted after sub-erythema-producing doses of irradiation. The maximal depression of blood pressure is gradually reached in about 24 hours, and low pressure values may persist for several days. This pressure drop appears to result partly from the reflex vasodilatation in abdominal viscera elicited by stimulation of afferent cutaneous nerves, which is triggered in some way by the changes associated with ultraviolet irradiation. Stimulation of the skin with irritants such as mustard oil can produce similar reflex vascular changes in internal organs. Curiously, the pulmonary circulation behaves reversely after cutaneous stimulation, as indicated by a correlated reduction in the blood content of the lungs.

In pathological conditions, especially tuberculous lesions, the patient's circulatory changes after intense sunbathing have often been noted in the form of focal hyperemic reactions. In patients with pulmonary tuberculosis, such reactions have led to profuse hemorrhages. In patients with lupus vulgaris, a variety of cutaneous tuberculosis, ultraviolet irradiation of uninvolved parts of the body surface has led to marked hyperemia of the lesions, even though they were kept covered during the irradiation.[29]

In dogs, the histamine content of the blood increases after ultraviolet irradiation, and, possibly, this phenomenon may contribute to the hypotensive effect of such irradiation.[30]

Among the other changes which have been correlated with ultraviolet irradiation are (1) a decrease in serum cholesterol,[31] (2) low, fasting-blood-sugar level and flat, glucose-tolerance curves,[32] and (3) a decrease in serum tyrosine.[33] It has been suggested that the latter reflects the accelerated utilization of tyrosine for increased melanin synthesis. In children, reduction of blood phosphatase levels and elevation of calcium values have also been reported.[34]

Comment

Mention should be made of the common feeling of increased health and physical fitness which people have after moderate exposures to sunlight. Even though it may seem that these feelings may be largely psychological in origin, there is the possibility (in this psychopharmacological age of tranquilizers and psychic energizers) that objective, sunlight-induced, biochemical alterations may also be somehow involved.

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CLINICAL SCIENCE

MEASUREMENT OF MYOCARDIAL BLOOD FLOW

RADIOISOTOPE TECHNIQUES USED IN PATIENTS WITH NORMAL AND ARTERIOSCLEROTIC HEARTS AFTER INFARCTION

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For over 100 years nitrates have been used as vasodilators. It is now almost 50 years since Meyer[1] showed that nitroglycerin caused dilatation of the coronary arteries of a dog. Subsequently, many nitrates have been used in a search for one with a longer duration of action than nitroglycerin. Of the nitrate compounds with prolonged action, pentaerythritol (Peritrate) tetranitrate, or PETN, has received the greatest clinical acceptance.

While coronary dilatation with nitrates has been objectively demonstrated in animals, a similar effect in human beings is less well documented, especially in those clinical situations in which these drugs have proved most useful. The failure to confirm the effectiveness of nitrates in the abnormal circulation of patients with arteriosclerotic heart disease results from the technical difficulty encountered in determining coronary blood flow in intact human beings.

Evidence that these drugs have a beneficial effect on coronary circulation in patients with arteriosclerotic heart disease has rested on the clinical effect of this class of drugs on patients with the anginal syndrome and their ability to reverse the effects of standard exercise on the electrocardiograms of patients with evidence of coronary insufficiency. With use of the standard Master two-step exercise test, Russek and co-workers[2] were able to show a reversal of the electrocardiographic findings produced by standard exercise for 15 to 30 minutes after the sublingual administration of nitroglycerin and for five hours after oral administration of PETN. When the coronary sinus is catheterized, nitrous oxide can be used to estimate coronary blood flow in human beings. Brachfeld and co-workers[3] were able by this method to demonstrate a 63% increase in coronary blood flow after the administration of nitroglycerin. However, Garlin and co-workers[4] failed to show an increase in coronary blood flow in patients with coronary artery disease.

Recently a new radioisotope method for the simultaneous measurement of coronary (myocardial) blood flow and cardiac output has been introduced. This method is quantitative and does not require coronary catheterization; hence, it is applicable to the estimation of myocardial blood flow in both normal and arteriosclerotic patients. We have used this method to compare the relative effect of two nitrates on the myocardial blood flow of normal

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subjects and patients with known myocardial infarctions.

Method

The radioisotope method used in this study has been described previously.[5] In brief, it consists of placing a scintillation detector on the chest wall where this detector can monitor the first passage of a radioactive bolus through the right and left sides of the heart and through the myocardial circulation. On the basis of the time activity curve obtained, it is possible to determine myocardial blood flow and cardiac output. Radioiodinated human serum albumin was used as the tracer substance to determine cardiac output. In all other curves, radioactive iodopyracet (Diodrast) was used as the tracer substance.

TABLE 1.—*Effect of Nitroglycerin and PETN on Coronary Blood Flow and Cardiac Output in Eight Female Patients (Group 1) with No Evidence of Cardiac Disease*

	Cardiac Output, Liters/Min.	Myocardial Blood Flow, Ml./Min.	Time After Medication, Min.
Control	5.40±0.13	367±28	...
Nitroglycerine, 0.6 mg.	5.02±0.27	522±43*	10
PETN, 20 mg.	6.73±0.51*	636±35*	90

* Statistically greater than control: $p < 0.01$.

Three groups of patients were used in this study. Group 1 was a control group, consisting of eight middle-aged women of average height and weight. These patients, hospitalized for psychiatric treatment, had no clinical or electrocardiographic evidence of myocardial or coronary artery disease. Group 2 was a control group consisting of 11 middle-aged men of average height and weight hospitalized for treatment of diseases not related to the cardiovascular system. This group by history, examination, and electrocardiogram also showed no evidence of cardiovascular disease. Groups 3 and 4 consisted of 10 patients, each diagnosed as having had previous myocardial infarctions. About 30% of these patients had angina on exertion at the time of the study. No patients in cardiac failure were included in these groups.

TABLE 2.—*Effect of Nitroglycerin and PETN on Cardiac Output and Coronary Blood Flow in Eleven Patients (Group 3) with Angina and Previous Myocardial Infarctions*

	Cardiac Output, Liters/Min.	Myocardial Blood Flow, Ml./Min.	Time After Medication, Min.
Control	4.65±0.16	158±14	...
Nitroglycerin, 0.6 mg.	4.65±0.41	232±23*	10
PETN, 20 mg.	4.45±0.39	178±13*	60

* Increase in myocardial blood flow statistically different from control: $p < 0.01$.

Myocardial blood flow and cardiac output were determined in each patient before and after the sublingual administration of 0.6 mg. of nitroglycerin and, similarly, after the oral administration of 20 mg. of PETN. Myocardial blood flow determinations were made 10 minutes after the administration of nitroglycerin and one, two, four, and six hours after the administration of PETN. No direct comparison of the relative potency of these two nitrates was sought for or anticipated, but attempts were made to discern only their individual effects on the cardiac output and myocardial blood flow in patients with normal and arteriosclerotic hearts.

Results

Table 1 shows the effect of two nitrates on the cardiac output and myocardial blood flow in group 1. The mean control cardiac output was 5.4 liters per minute, while PETN produced a significant increase in cardiac output in this group. The mean control myocardial blood flow was 367 ml. per minute. This increased to 522 ml. per minute 10 minutes after administration of nitroglycerin and to 636 ml. per minute 90 minutes after the ingestion of PETN.

Table 2 demonstrates the effect of the drugs on cardiac output and myocardial blood flow in patients of group 3 who had clinical evidence of coronary artery disease. In these 11 patients, the mean control cardiac output was 4.65 liters per minute. The mean cardiac output was essentially unchanged by the drugs. Control cardiac output in this group is significantly lower ($p < 0.05$) than that observed in group 1. The mean myocardial blood flow was 158 ml. per minute; this increased to 232 ml. per minute 10 minutes after administration of nitroglycerin and 178 ml. per minute 60 minutes after that of PETN. These increases in myocardial blood are statistically significant ($p < 0.01$). Myocardial blood flow was about 50% less in this group than in group 1.

TABLE 3.—*Effect of Nitroglycerin and PETN on Cardiac Output in Ten Patients With and Eleven Patients Without Coronary Artery Disease*

	Drug				
	PETN				Nitroglycerin
Time, Hr.	1	2	4	6	1/6
Group 2 (control)	98*±4	101±6	95±5	107±10	91±6
Group 4 (arteriosclerotic)	101±5	103±6	105±4	101±6	92±4

* Percentage of control cardiac output; mean ± standard error of mean.

In table 3 the time action curves of PETN and those of nitroglycerin in groups 2 and 4 are compared. The percentage of the control cardiac output is recorded on this table at one, two, four and six hours after the administration of PETN. No change in cardiac output occurred after administration of these drugs to normal and arteriosclerotic patients.

Table 4 shows the effect of PETN and nitroglycerin on myocardial blood flow in these same groups, 2 and 4. The results are presented as percentages of cardiac output. Again, there is a statistically significant difference between the myocardial blood flow in the normal and arteriosclerotic groups. Both drugs produced significant increases in myocardial blood flow ($p < 0.05$). PETN, while producing a somewhat smaller increase in myocardial blood flow than nitroglycerin, was active within one hour after administration and lasted beyond four hours.

Comment

These studies demonstrate a 50% decrease in mean myocardial blood flow in patients with coronary artery disease not on therapy. This is similar to the results obtained by Bing[6] with the nitrous oxide method but contrary to the findings of others, which showed no difference or perhaps a slight increase in myocardial blood flow in coronary artery disease.[4] Previous work in dogs has shown a fairly good correlation between the nitrous oxide and radioisotope methods.[5] Simultaneous studies made with use of these two methods have not been done in patients with coronary disease; hence, care should be exercised in interpretation of the differences found by these two methods. There is ample evidence to show that nitrates increase coronary blood flow in animals and similar changes have been observed in man.[7] Furthermore, there is electrocardiographic evidence that the nitrates reverse stress-induced changes in patients with coronary insufficiency.[8]

Table 4.—*Effect of Nitroglycerin and PETN on Myocardial Blood in Ten Patients With and Eleven Patients Without Coronary Artery Disease*

	Drug					
	PETN					Nitroglycerin
Time, Hr.	0	1	2	4	6	1/6
Group 2 (control)	5.1*±0.4	6.5±0.8	6.1±0.5	6.0±0.8	4.53±0.5	6.8±0.5
Group 4 (arteriosclerotic)	3.4*±0.3	4.6±0.6	5.1±0.5	4.8±0.5	3.6±0.4	7.2±1

* Myocardial blood flow expressed in percentage of cardiac output.

While nitrates seem to decrease myocardial blood flow in patients with arteriosclerotic heart disease as measured by the nitrous oxide method,[4] the present study demonstrates significant increases in myocardial blood flow in arteriosclerotic patients after the administration of nitrates. This effect endures for better than four hours after administration of PETN and is present 10 minutes after the sublingual administration of nitroglycerin. It is reported that PETN produces a clinical effect within one hour after ingestion which lasts for five hours.[8] Time activity studies reported here confirm this observation. Results in group 1 suggest that the time of maximum activity of PETN is about 90 minutes after administration.

In all groups of patients, normal and arteriosclerotic, a significant correlation ($r = 0.68$) was found between the increase in coronary blood flow produced by nitroglycerin and that produced with PETN. Two of the patients did not respond to either drug. One patient responded to nitroglycerin and not to PETN. Thus, it might be possible to anticipate, from the short-acting clinical response to sublingually given nitroglycerin, the clinical usefulness of PETN in any individual patient.

Summary

The effect of a long-acting and a short-acting nitrate compound on myocardial circulation and cardiac output in patients with and without arteriosclerotic heart disease was tested with use of a newly devised method for measuring myocardial blood flow. Myocardial blood flow is significantly (50%) decreased in patients with coronary artery disease who receive no therapy. A significant correlation exists between the response, in terms of increased myocardial blood flow, to sublingually given nitroglycerin and that to orally given pentaerythritol tetranitrate (PETN) in individual patients. Ten minutes after the sublingual administration of 0.6 mg. of nitroglycerin, there is an increase in myocardial blood flow, without change in cardiac output, in patients with arteriosclerotic heart disease. PETN produces a prolonged increase in myocardial blood flow beginning within one hour after ingestion and lasting up to five hours, without producing changes in cardiac output, in patients with arteriosclerotic heart disease with previous infarction.

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MEDICAL SPELEOLOGY

THE hobbies of a "thinking" physician most surely cover as broad an area as any other type of thinking man. Speleology is one avocation that is not associated usually with the practice of medicine, or, for that matter, with any other pursuit in life except for the enrichment of the speleologist. Similar to philately with its special geographic tropisms, the amateur speleologist may concentrate on the exploration of caves in a selected geographic area. William R. Halliday,[1] a thoracic surgeon in private practice in Seattle, has pursued his underground ventures, methodically and seriously throughout the western United States for more than a decade. During and after his formal surgical training, Halliday deserted temporarily and periodically professional friends and family to prowl in the bowels of the earth. Having chosen the anatomy above the bowels of man for his surgical interest, he chose not to forsake the inner passages of the earth during week ends and holidays.

The number of caves that are open to the public and are available for limited observation is not great. The number of caverns on private or government-owned land is legion. Insatiable curiosity and an adventuresome spirit are basic requisites for the spelunker. The equipment includes the paraphernalia of the mountain climber as well as the underwater gear of the Scuba devotee. Ropes, rappeling pads, and pitons, the symbols of cragmanship, are as necessary as oxygen masks, tanks, and waterproof suits for underwater exploration. Bats, stalactites, stalagmites, helictites, dripping water, and deathening darkness may be encountered not far from the entrance of a cave.

The bat, a rat-like animal with wings and sonar, was considered to be the ideal conspirator for an interesting and novel experiment in World War II. Doctor Lytle S. Adams, a dental surgeon, conceived the idea of equipping millions of bats with tiny thermite bombs and releasing them by parachute over enemy cities in daylight. The bats would seek dark, inaccessible hiding places at once, chew off the string that held the bomb, and before long the incendiaries would start a conflagration. The bat is capable of carrying three times its body weight in flight. Preliminary experiments revealed the validity of the proposal. The batty plan worked. The bats lost their chance to become vertebrate heroes like the K-9 Korps by the sudden surrender of Japan.

There are a number of mortuary or bone caves in central California. Some of the bones have been judged by isotope studies to be more than 3,500 years old. The most famous cave in this category is the Cave of the Catacombs. The Moaning Cave, one of the largest ossuaries, has given up more than 25 human skeletons. By means of carbon-14 studies, one amateur speleologist estimated the skeletal remains in this cave to be at least 12,000 years old. This claim has been stoutly refuted by others, due to the varying rate of deposition of speleothems. The deepest cave in America, according to Halliday, is the Neff Canyon in the Wasatch Mountains near Salt Lake City. It has been explored to a depth of 1,186 ft. over a similar longitudinal distance. The existence of this cave was not known until 1948, when some schoolboys discovered it on a hike. The cave has no commercial value and cannot compete in accessibility, beauty, or grandeur with the Carlsbad caves, the Caves of Luray in Virginia, the Mammoth caves in Kentucky, or even the Cave of the Winds in Colorado, four of the more popular caves in the continental United States.

The glacier caves and the lava tubes of the west are strangely similar. The formation of each has been due to the pressure of flowing substances under the influence of gravity. Flowing ice furnished the energy for the formation of the ice caves, molten rock for the formation of the lava tubes. The latter are found in the vicinity of volcanoes which have been active, without spectacular eruptions. The molten 'pahoehoe' lava, or liquid rock, flows from the center of the volcano to the periphery. The undersurface and the crust cool faster than the core. At a critical temperature the circumference of the flow solidifies, but the center continues, leaving a tube, often the size of a subway tunnel, in its wake. Some of the most accessible lava tubes are in the Lava Beds National Monument in northeastern California near Mount Lassen, the volcano that last erupted in 1915.

Are you interested in speleology? It might be profitable to learn the "spiel" of the spelunker. Aa, belay, corynorhinus, dripstone, duckunder, glaciere, gour, karabiner, littoral, myotis, palette, pisolite, prussik knot, speleo-historian, and troglodytic are terms defined by Halliday in his glossary.

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[1] Halliday, W. R.: Adventure is Underground, New York, Harper & Brothers, 1959.

HEAT PYREXIA

The study on heat pyrexia (heat stroke) in this issue of THE JOURNAL, p. 1175, is a derivative of human physiological research in hyperenvironments, conducted at the Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio. The Air Force has long been interested in the effects of extreme heat on crews of high-performance aircraft and of spacecraft to come. As a result, a comprehensive study was launched a few years ago in which it was hoped to learn the stepwise effect of quantitative loads of heat—to the point of clinical heat stroke—upon healthy, unanesthetized humans. That this could be done was principally due to two factors: the availability of human volunteers and the uniqueness of the environmental chambers at this laboratory. These chambers can simulate practically any combination of temperature, humidity, air motion, and even air pressure.

For the main part, thermal exposures were at a level of 130° F (54.4° C) and 8% relative humidity for two hours, and 160° F (71.1° C) and 4% relative humidity for one hour; however, in some cases, greater extremes were resorted to. Studies included body heat storage and effective body heat storage, direct venous pressure, cardiac output and blood gas analyses, sweat rate determinations, sweat replacement experiments, oxygen consumption, cardiac shadow measurements, auscultatory examinations, electrocardiogram abnormalities, blood pressure responses, and hemoconcentration and osmolarity determinations. It was hoped that these studies would help shed knowledge on some of the major unsolved enigmas of heat stroke: 1. What causes the circulatory collapse seen in this disease? 2. Why do patients stop sweating? 3. Why are older subjects more susceptible to this syndrome? and 4. What is the most effective means of reducing the pyrexia?

For reasons clearly delineated in the text of the study itself, a working theory on the development of heat stroke was formed. It conceives of the circulatory collapse as a resultant of a high-output type of cardiac failure. Indeed, the entire syndrome may be due to this triggering mechanism. The cessation of sweating is correlated (and indirectly attributed) to a rise in venous pressure; and, conversely, the restoration of the sweating mechanism is correlated with a return to normal of venous pressure. Older persons are found to be more susceptible because they absorb more heat from a given thermal exposure. The reason is that, by the time they reach 45 years of age, their circulatory systems (the chief means of heat dissipation) have already become compromised and can no longer undergo a full range of compensatory adjustments. Finally, it is hypothesized that the intravenous administration of saline solution together with rapid digitalization, in conjunction with the more classical methods of rapid body cooling, may be lifesaving.

RENAL TRAUMA: TWO-HEADED MONSTER

In this issue of THE JOURNAL, p. 1189, appears an article dealing with "The Injured Kidney." Injury to the kidney is unquestionably more common than we suspect, since many instances may be relatively minor in nature and thus overlooked. The sociologic factors of high-speed transportation, enthusiasm for contact sports, and leisure time to indulge in some rather hazardous hobbies are prevalent and increasing. It seems not unlikely that the opportunities for kidney injury may also become more frequent. An analysis of kidney injuries leads to the inevitable observation that there are two major aspects of the problem: the first is the diagnosis and management of the acute renal injury; and the second—perhaps more important but less appreciated—is the recognition of the late complications of renal trauma.

The diagnosis of acute renal injury depends upon an awareness of the possibility of injury and upon the indicated studies. Physical examination and urinalysis may be definitive, but it is usually necessary to obtain radiographic confirmation of the diagnosis. A plain roentgenogram of the abdomen is only occasionally diagnostic of severe renal injuries and is never an aid in establishing the presence of more subtle trauma. Excretory urography can only be diagnostic if satisfactory concentration of and filling by the medium are obtained. Many physicians, including some urologists, are reluctant to employ retrograde pyelography, the single most helpful diagnostic tool.[1] This reluctance undoubtedly is born of respect for the possibilities of infection and hemorrhage, but, with skillful manipulation, rigidly aseptic technique, and appropriate antibiotic therapy, these risks should be even more negligible than in previous eras of less adequate facilities.

If the patient suffering from renal trauma is to be managed effectively, all personnel in attendance—professional and nonprofessional—must have an appreciation of the implications in any kidney injury. The patient with extensive injury will obviously require more care and observation than one with only minor trauma. It therefore is essential that physicians employ a consistent method of classifying and managing renal injuries. Admission diagnoses of "renal abrasion," "contusion of the kidney," and "fractured," "fragmented," or "shattered" kidney are colorfully descriptive but may hold little meaning for the average ward attendant. However, a diagnosis of "renal injury, severe" should alert all involved to the gravity of the situation. A practical and convenient classification of kidney injuries is presented in the current article. It is predicated upon adequate radiologic study of the patient with renal trauma, a prerequisite to good management. It cannot be stressed too emphatically that this management must be based upon thorough evaluation as well as the realization that hasty surgical measures may result in irrevocable damage as often as will uninformed complacency.

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[1] Lynch, K. M., Jr.: Traumatic Urinary Injuries: Pitfalls in Their Diagnosis and Treatment, J. Urol. 77:90-95 (Jan.) 1957.

[2] Page, I. H.; McCubbin, J. W.; and Corcoran, A. C.; Guide to Theory of Arterial Hypertension, Perspectives Biol. M. 1:307-325 (Spring) 1958.

The late complications of renal trauma comprise the second aspect of the problem. Although the minimally injured kidney rarely shows permanent damage, it is not uncommon for the severely or moderately traumatized kidney to develop scarring, infarction, cystic degeneration, perirenal abscess, calculi, hydronephrosis, or atrophy. Permanent radiographic evidence of renal damage may be found in as many as one-tenth of all injured kidneys, and such anatomic changes can produce physiologic abnormalities of renal function. Progressive renal insufficiency may ensue if the contralateral kidney is abnormal. However, the most important sequel to permanent renal damage is hypertensive vascular disease, occurring in great enough frequency to demand our attention. The exact nature of such hypertension cannot be stated, but it appears likely that the Goldblatt humoral mechanism is evoked: renal parenchymal and/or vascular damage may result in relative renal ischemia, with subsequent renin production, followed by systemic conversion by renin of angiotensin which is thought to induce the vascular hypertensive response.[2] In any event, the recognition of these sequelae of renal injury depends upon an adequate follow-up. The "well" patient's natural abhorrence of return visits must be overcome by acquainting him with the potentialities of his injury, and the physician in turn must perform postinjury pyelography, blood pressure checks, urinalyses, and, in selected cases, renal function studies. The mandatory follow-up in any kidney injury should be three months, and no less than a one-year period of follow-up should suffice in the patient suffering severe renal trauma.

It seems reasonable to assume that the injured-kidney "monster" will assume larger proportions: more renal trauma may be sustained, and more physicians will be alert to that possibility. If the monster is to be dealt with effectively, both "heads" must be attacked logically and persistently.

A NEWSWORTHY EVENT

Because every physician who has prepared a communication for J. A. M. A. devotes a portion of his time and talent in advancing the medical profession, it has occurred to us that it might be appropriate to devote some space to one of the new, though less spectacular services, which is now available to authors.

Proximity makes an event newsworthy. Add nearness of time to nearness in personal concern, and you may understand our reasons for appraising the availability of tear sheets as a newsworthy event.

Authors will receive upon request 50 complimentary copies of their communication. They will be in tear sheet form, stapled and without covers.

We trust that this service will fill many needs. In some instances, the availability of tear sheets may supersede the need for reprints. However, we will continue to prepare and make reprints available upon request as has been done in the past.

WEGENER'S GRANULOMATOSIS

In considering the history of diseases, this syndrome has more recently been separated from the diseases of connective tissue for diagnostic and prognostic reasons.

This disease was first recognized by Klinger[1] in 1931, but Wegener,[2] in 1936, described and characterized the features which distinguish this condition. In 1954, Fahey and his associates[3] more clearly established the clinical and pathological findings. Since then there have been increasing reported cases in Europe and the United States.

Wegener's granulomatosis has had a difficult path in this short period, because the identifying characteristics of this disease resemble many conditions and invade many systems. No doubt, this has retarded its establishment as a separate entity and continues to frustrate clinicians in their differential diagnosis.

The plethora of terms applied to what is now known as Wegener's granulomatosis gives an idea of the protean nature of this process: necrotizing granulomatosis and angitis, respiratory-renal type of polyarteritis nodosa, pathergic granulomatosis, atypical periarteritis nodosa, giant cell granuloma, rhinogenous granuloma, rheumatic vascular inflammation, pararheumatic disorder, Löffler's syndrome, hemorrhagic and interstitial pneumonitis with nephritis, and allergic granulomatosis. In this issue of The Journal, p. 1205, is an article entitled "Wegener's Granulomatosis, A Triad," which appears to be a likely guide and should prove helpful for a finger-tip diagnosis in the detection of this disease.

As a syndrome, Wegener's granulomatosis can be differentiated from other categories of arteritis and granulomatous diseases by the following clinical and pathologic changes: 1. The rather simple onset of the disease is insidious, with rhinitis and sinusitis, eventually leading to granulomatous destruction of the nasal passages and granulomas of the lungs.

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[1] Klinger, H.: Grenzformen der Periarteritis Nodosa, Frankfurt. Ztschr. f. Path. **42**:455-480, 1931.

[2] (*a*) Wegener, F.: Uber generalisierte, septische Gefasserkrankungen, Verhandl. d. deutsch. path. gesellsch. **29**:202-210, 1936. (*b*) Wegener, F.: Uber eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren, Beitr. z. path. Anat., u. z. allg. Path. **102**:36-68, 1939.

[3] Fahey, J. L.; Leonard, E.; Churg, J.; and Godman, G. C.: Wegener's Granulomatosis, Am. J. Med. **17**:168-179 (Aug.) 1954.

2. The vasculitis is generalized but is most severe in the respiratory tract and the kidneys. 3. Mild albuminuria, microscopic hematuria, and casts reflect the glomerulonephritis, heralding the inevitable terminal uremia. When the "triad" is completed, dissemination of the disease is accomplished.

Antemortem diagnosis depends primarily on the combined clinical, radiographic, and laboratory findings. Cytologic studies from sputums, endoscopic smears, and biopsies from sinuses, larynx, and trachea are confused by secondary bacterial invasion. Exploratory thoracotomy for biopsy may render chronic granuloma, with or without vasculitis. Renal biopsy will demonstrate glomerulonephritis. When evaluation of the patient as a whole is considered with the aforementioned aids, a proper diagnosis may be obtained by the clinician and pathologist.

Therapeutic measures and prognosis are determined by the progress of the disease. X-ray therapy to the nasal cavities and lungs is helpful. The addition of steroids to x-ray therapy facilitates temporary remission. Steroid therapy alone appears to repress the vasculitis at times. Antibiotics are useful in combating secondary bacterial invasion.

It appears there is an approach that will offer benefit to the patient, despite the ultimate prognosis.

CARDIOVASCULAR DISEASE IN CAUCASIANS AND NEGROES

In the statistical study of human disease, such factors as age, sex, and race need explicit evaluation. Of these, the racial factor perhaps has been the most frequently neglected and misinterpreted. That this may prevent the more complete understanding of disease has been pointed out in a recent review[1] on this subject with particular reference to the cardiovascular system.

In the evaluation of the racial factor in disease, a scientific point of departure is mandatory. This lies not in the color of the skin but in the genetic background reflected in this skin color as well as in other factors. Racial features such as pigmentation provide a basis for grouping, selection, and propagation of certain underlying genetic characteristics. It is on the characteristic genetic foundation, then, that racial differences in the interactions and expressions of disease processes become possible. The disease may be the same, but the somatic substrate on which it acts accounts for the manifestations which we observe. Other factors, such as geographical location, socioeconomic level, and religion may provide a basis for grouping and propagation of certain genetic characteristics, but on a large, overall scale the most important factor appears to be race.

The statistical evaluation of racial factors in disease is not an easy task. Numerous variables of necessarily large series must be properly controlled, and many attractive pitfalls must be conscientiously avoided. Most of the relevant data have been supplied from large hospital series or from statistical reports by governmental agencies and insurance companies. Such factors as the simple definition of a disease may cause wide variation in the interpretations and conclusions from different series. Obvious comparative difficulties arise from terminology; for example, hypertension, hypertensive heart disease, hypertensive arteriosclerotic cardiovascular disease with and without renal disease, arteriolar hypertension, systolic hypertension, diastolic hypertension, and others. Not only the definition of the terminology but quantitative evaluation of the severity of the disease process is important but difficult. For example, how many atheromatous plaques constitute significant arteriosclerotic disease? In addition to this consideration, the location of the particular disease process is important. Some investigators may consider a small plaque in a coronary artery to indicate more severe atheromatous disease than a much larger plaque in the abdominal aorta, but others may not. Furthermore, in comparing racial groups one cannot simply rely on the broad diagnosis of atheromatosis or arteriosclerosis. Significant racial differences may be apparent for patients with arteriosclerotic coronary artery disease but not for those with arteriosclerotic peripheral vascular or cerebral vascular disease.

Additional considerations are necessary when evaluating and comparing series in attempts to study racial determinants in disease. Such factors as changes in disease patterns through the years in response to public health measures, better diagnostic facilities, and earlier therapy must be analyzed in their proper perspective. The impact of antibiotics has caused a great change in the relative racial patterns of disease. Syphilitic heart disease is an outstanding example. Other, but no less important, factors deserving consideration in the statistical evaluation of various institutional studies are racial admission rates to hospitals, racial autopsy rates, selective factors operating locally, and methods of investigation.

Racial differences in disease manifest themselves in one or more of several spheres of study, such as the incidence of the particular disease, its pathological or clinical expression, its morbidity, or its mortality. Consideration should be given not only to these racial differences in response to disease but also to differences in basic anatomy, physiology, and pharmacology.

As might be expected, the results and conclusions of different reports dealing with racial factors in disease states at times have shown wide variation. Usually, however, these variations are matters of degree or magnitude and not of direction. Thus, the direction of conclusions relating to racial differences has been remarkably similar from study to study. For these reasons, the recognition of racial influence in any investigation dealing with human subjects appears important.

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[1] Phillips, J. H., and Burch, G. E.: Review of Cardiovascular Diseases in White and Negro Races, Medicine 39:241 (May) 1960.

The influence of man's environment on the racial incidence of cardiovascular disease is poorly understood but known to exist. An example in point is that the incidence of coronary disease in Negroes in Africa is considerably less than that in Negroes in the United States. Whether the important factors operating here are dietetic, climatic, or related to superimposed disease, physical or emotional stress, or other conditions is unknown. The ways in which man's environment influences his health obviously require further study.

After an extensive survey of the literature dealing with cardiovascular diseases in Caucasians and Negroes,[1] certain conclusions based on the reported data could be reached. Apparently, hypertensive disease in American Negroes occurs significantly more frequently and with greater morbidity and mortality than in American Caucasians. In contrast, arteriosclerotic heart disease is more common in Caucasians. Pathological study has shown that the rate of development of coronary atheroma in Negroes is slower by about 10 years than it is in Caucasians. Of interest is the fact that the ratio of Caucasoid males to females for this disease was much greater than the ratio of Negroid males to females. With respect to aortic, cerebral, or peripheral vascular arteriosclerosis, significant racial differences were not apparent.

The incidence of rheumatic fever and rheumatic heart disease is greater in Caucasians, but there is a distinct tendency for Negroes, once they have developed the disease, to run a more severe and more prolonged course, to have more residual heart damage, and to die at an earlier age. Congenital heart disease is almost twice as frequent in Caucasians, while syphilitic cardiovascular disease is about four times more frequent in Negroes.

Significant racial differences were noted to occur in relation to several other cardiovascular diseases. The following states were found to occur in Caucasians more than five times as frequently as in Negroes: thromboangiitis obliterans, multiple hemorrhagic hemangioma of Kaposi, glycogenic tumors of the heart, hereditary hemorrhagic telangiectasia, temporal arteritis, histaminic cephalgia, erythromelalgia, cardiac amyloidosis, muscular dystrophy with heart involvement, and the Wolff-Parkinson-White syndrome. Cardiovascular diseases apparently occurring with a significantly greater incidence in Negroes were sarcoid heart disease, tuberculous pericarditis, angiomesohyperplasia, vascular injuries due to cold, and ainhum.

The magnitude and constancy of the racial differences occurring in many of the diseases mentioned above seemed to exclude the possibility that these differences were due to selective factors, faulty sampling, or chance alone. Since these differences do occur, it appears important to reemphasize that the racial factor should be critically evaluated in statistical studies dealing with human subjects.

TONICS AND SEDATIVES

The replacement of Tonics and Sedatives by Medical Satire or other narratives in selected issues of THE JOURNAL, an innovation that was begun early this year, has flushed a modest number of letters from the calligraphy coves of physicians and lay persons. Three communications that were received in this office were composed by nonmedical personnel who were accustomed to seek solace or financial gain in the perusal, or revision, and reuse of selected excerpts of the comic section of THE JOURNAL. The objection to the substitution was unanimous from this area. The letters received from physicians, however, expressed varied opinions. Several, who by confession or by my consultation with the A. M. A. Directory for vital statistics, deplored the loss of their weekly smiles that dated from the early decades of this century. An equal number favored the satirical discourses, particularly "Latinonian Exchange" (*J. A. M. A.*, February 27, 1960) and "Peniwisle" (*J. A. M. A.*, March 12, 1960).

The persistence of this succedaneous action will be contingent upon two phenomena, one negative, one positive. The voice of many physicians raised against the change will not be ignored permanently. Equally vital will be the quality and quantity of medical satire and narration available for publication. About one-half of the communications that have been received during the past four months in this category have been submitted without solicitation. If this percentage is maintained or increased, there will be no need to sound the alarm. I suspect that this will be factual. Meanwhile, as physicians or lay persons reveal their shrift for brief buffoonery, "The Bright Side" continues to appear weekly in THE JOURNAL. Also, Dr. Thomas Richard Rees,[1] a physician practicing in Washington, D. C., offers a full collection of witticisms from the past issues of THE JOURNAL and other sources. Being particularly fond of limericks, there are two items of humor selected by Rees that can be reproduced in these pages without danger of transgression of postal regulations regarding the interstate transmission of obscene literature.

"The Lord gave us two ends to use,
One to think with, one to sit on.
It all depends on which you choose—
Heads you win, tails you lose."

"Here lies the body of Teddy Tites
Who never offered to dim his lights;
The onrushing car came in with a roar,
And dimmed his lights forever more."

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1. Rees, T. R.: I Prescribe Laughter, New York, Vantage Press, 1960.

COUNCIL ON NATIONAL SECURITY

DISASTER-SCALE MEDICAL CARE PROBLEMS

A STUDY OF MEDICAL MANAGEMENT OF CASUALTIES RESULTING FROM A TORNADO IN DALLAS, TEXAS

John W. Raker, M.D., Boston
and
Hiram J. Friedsam, Ph.D., Denton, Texas

Medical preparedness for disaster too frequently is associated with nuclear warfare and a staggering casualty problem of inconceivable proportions. Actually, many other types of disaster daily threaten our civil way of life. The following paper describing a study of the medical care problems experienced in a tornado supports the need for medical preparedness for the carrying out of emergency operations to cope with all kinds of disasters, including protection and survival in an all-out war.
Frank W. Barton, *Secretary*

At approximately 4:20 p. m. on April 2, 1957, a tornado struck the western portion of the city of Dallas, Texas. The storm coursed northward through several residential areas of varying population density and followed a path approximately 16 miles long. It was moving sufficiently slowly that a great number of the people of the city were able to watch its advance; it was visible for about 45 minutes. The progress of the tornado was unusually well documented by the use of mobile radio-broadcasting trucks, and numerous motion pictures and still pictures were made. These records have been circulated widely, and they have aroused great interest in this disaster.

Because of the widespread feeling in Dallas that the medical care rendered to the casualties of this tornado was of an extremely high caliber, an invitation was issued to representatives of the Committee on Disaster Studies of the National Academy of Sciences–National Research Council (now Disaster Research Group) to enter the Dallas area and conduct a study of the medical care aspect of the disaster.

The City and Its Plan for Disaster Control

Dallas is the second largest city in Texas. The 1950 census figures show 434,462 people within the city limits and 614,799 people in the entire metropolitan area. By 1957 it was estimated that the population of the metropolitan area exceeded three-quarters of a million people. The city is a major wholesaling and distribution center for the economic life of the southwest, and it also serves as a major financial center for this region. In general the industrial development is light, and a number of the factories are distributed along the course of the Trinity river which flows from northwest to southeast through the center of the city. The main business district and the larger residential areas lie east of the river. Roughly two-thirds of the total length of the tornado's path was west of the river in the residential areas of Oak Cliff and West Dallas. The remaining one-third of the storm's path was east of the river but several miles north of the main business district.

The social service and relief agencies of the city were similar to those of other cities of comparable size; however, certain arrangements in the interrelationships of these organizations were probably unique to Dallas, Texas or at least to the southwestern area of the United States.

In 1954 a Civil Defense and Distaster Commission for the city as well as the county of Dallas was established. This commission consists of the mayor, the city manager, the county judge (exofficio), and a number of appointed members. The chairman, three vice-chairmen, and three other members represent the important business and professional interests of the city.

This committee has established elaborate plans for the handling of the various aspects of civilian disaster. The director of the activities of the commission makes his headquarters in the fairgrounds of Dallas, in the immediate vicinity of the large football stadium known as the Cotton Bowl. At the time of the tornado the medical activities of the Civil Defense and Disaster Commission were entrusted to the supervision of the second vice-chairman of the commission, a physician. This same physician was a member of the Disaster Relief Committee of the Dallas County Chapter of the

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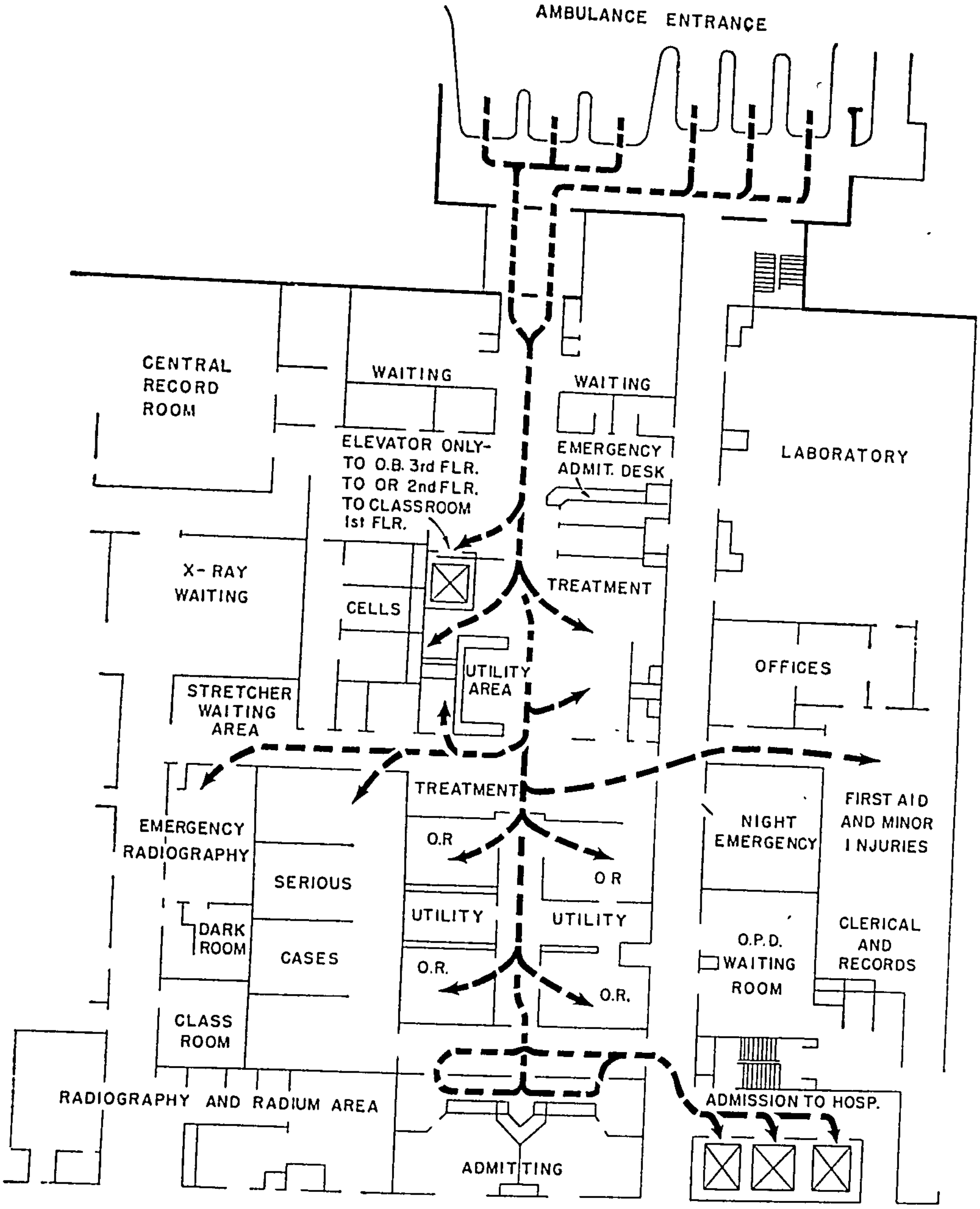
From Surgical Service, Massachusetts General Hospital, Boston (Dr. Raker); Department of Sociology, North Texas State College, Denton (Dr. Friedsam).

American Red Cross and held the responsibility for medical and nursing care and first aid activities of the Red Cross. Serving with him on the Health Committee of the City-County Civil Defense and Disaster Commission were a hospital administrator and four other physicians, one of whom represented the Dallas County Medical Society. These organizations had planned that the fundamental responsibility for the care of casualties in case of disaster would rest with the Health Division of the Dallas City-County Civil Defense and Disaster Commission. This responsibility was to include the provision of first aid and transportation to the hospitals.



The floor plan of Parkland Memorial Hospital, with diagram of patient routing procedure used in handling casualties of tornado disaster.

The relationship between the police and the ambulance system of Dallas is characteristic for many cities in Texas and nearby states; in that area, it is common practice to have ambulance facilities owned and operated by directors of funeral homes. One of the funeral homes has a contract which makes it responsible for the provision of ambulance service in the entire city, and it covers an area in its immediate neighborhood with its own ambulances. Several other funeral homes have subcontracts to provide service for their respective areas; in this fashion, the entire city is serviced. When a hospital receives a request for ambulance service, the police dispatcher is called. The police dispatcher calls the appropriate funeral home by direct line and orders an ambulance to be sent to the patient's address.

In addition to the 92 ambulances available in the 31 funeral homes of Dallas County, there were hearses and flower trucks available for use in disaster. Of all these vehicles, at least 23 had some form of radio communication. In the plans of the City-County Civil Defense and Disaster Commission, the control of ambulance service in case of disaster is under the direction of the owner and operator of one of the largest funeral homes of the area.

In addition to the ambulance service provided in this fashion, there are a number of rescue squads which have been organized under the rescue section of the City-County Civil Defense and Disaster Commission and are immediately responsible to the chairman of the rescue section. Many of these rescue squads and trucks are associated with industrial plants. There has been an attempt to conduct a training program for these rescue squads over the last several years.

Also available is a volunteer group called the Dallas Emergency Corps, which responds to calls for first aid and rescue activities. All of these organizations can be reached by the police dispatcher, directly or indirectly.

Another outstanding feature of the arrangements made before the tornado disaster in the city of Dallas was the consideration which had been given to the planning of the physical plant of Parkland Memorial Hospital in order to orient it toward effective function in case of disaster (see illustration). Parkland occupies a unique position among the hospitals of the city because it is operated under an amendment to state laws which created "hospital districts" and permitted local authorities to use tax money raised locally for their operation. Parkland's "district" was established about 1950, and the hospital now operates with a surplus, in spite of the fact that it provides almost all of the charity work done in Dallas. The hospital's work includes more than 90% charity cases. The remaining hospitals of the city have a very low burden of charity work, and the trustees of the private hospitals are sympathetic to the aims and purposes of Parkland. There are separate facilities for Negro and white patients, and it seems to be the accepted fact that most of the Negro patients in the city will be cared for at Parkland. The Board of Trustees of Parkland Memorial Hospital, operating under the "hospital district" arrangement, has a very liberal financial policy toward its charity work.

The hospital was completed in 1952, at a cost of 10 million dollars. The physical planning was made with the prospect of caring for large numbers of emergency patients in mind. Most of the medical emergencies in Dallas are now treated at this hospital, and this fact is generally accepted by the police dispatcher, ambulance drivers, other hospitals, and the populace at large. In event of disaster the plan of the Health Committee of the Civil Defense and Disaster Commission is that Parkland is to receive casualties until its capacity is reached and only then are the casualties to be diverted to other hospitals.

The hospital is adjacent to and associated with the Southwestern Medical School. The medical students and nursing personnel associated with the hospital usually live nearby and are readily available in case of an emergency. There is a small full-time clinical staff as well as a house staff of 130 residents and interns.

The emergency ward at Parkland usually cares for 200 patients in a normal operating day. Most of these patients are admitted at night. There are spaces at the emergency ward door for six or eight ambulances with which to discharge patients. At the emergency ward admitting desk, there is an immediate physical separation of visitors, relatives, and volunteers from the patients. The patients are admitted to the ward, and all other persons are placed in waiting rooms near the entrance.

Because of the liberal financial policies in effect when Parkland was built and because its administrator, Mr. A. H. Scheidt, was conscious of the need, the hospital was planned so that there could be expansion of its physical facilities in time of disaster. There are four operating rooms in the emergency ward, and the space assigned to patients can be expanded rapidly into adjacent corridors and rooms otherwise used for access to hospital's admitting offices and to the classrooms of the nursing school. The emergency ward has a special x-ray facility immediately available to it. If the load becomes too great for this facility, provision is made for the x-ray work to be done in available rooms adjacent to the regular x-ray department. Elsewhere in the hospital there are large classrooms, lecture halls, and waiting rooms, all equipped with facilities to provide for additional patient care in times of emergencies.

Tornado and Resultant Damage

The tornado track was only 50 to 200 yards in width, and the funnel cloud was moving at about 20 miles per hour. From the section of Oak Cliff where the tornado first struck and along the first six to eight miles of its path, the storm was traversing predominantly middle-class white residential areas. In this section damage was relatively light, and casualties were relatively few. The storm then crossed an industrial district and caused considerable property damage. It entered West Dallas section at a point where a Negro residential area is located. (This happens to be an area which houses a lower scale socio-economic group.) Both property damage and casualties were relatively heavy in this district, partly because of the flimsy nature of the housing. The funnel cloud then moved across the Trinity river and smashed into a second Negro residential area called Record Crossing. Although housing in this area was somewhat better and newer than in the West Dallas section, property damage and casualties were again comparatively heavy, probably the heaviest of any area in the tornado's path. From the Record Crossing section the tornado moved across another industrial center (inflicting relatively light damage) and into another middle-class white residential neighborhood, where again casualties were few. Shortly afterward, the funnel cloud lifted and disappeared. Its direction of movement through the city had been generally north, and, in the last few miles of its journey, somewhat northwest.

At the end of the week the Red Cross summarized the damage caused by the tornado as follows: [1] dwellings destroyed, 118; dwellings with major damage, 112; dwellings with minor damage, 332; small business houses destroyed, 24; small business houses damaged, 15; churches destroyed, 4; churches damaged, 1; apartments destroyed, 9; and apartments damaged, 3.

The approximate number of those injured and killed was 202. Of these, 7 persons (dead on arrival) and 170 (injured) were received at Parkland Memorial Hospital. Forty-one of the more seriously injured persons were hospitalized at Parkland. According to figures from Methodist Hospital, 18 persons were seen at that institution. There were 6 hospital admissions; 1, dead on arrival; and 11, treated and released. The other hospitals of Dallas received no more than one or two patients each and apparently did not admit any. All Negro patients were admitted to Parkland.

Disaster Plan Tested

Notification and Communication.—On April 2, 1957 it was hot and still in Dallas, Texas. During the day a tornado alert had been broadcast by the United States Weather Bureau. Such warnings had been made approximately 100 times in the previous year, and none of the serious alerts had been followed by the appearance of a serious storm.

A few minutes before 4 p. m. the sheriff of the small town of Duncanville, Texas (approximately 12 miles to the southwest of Dallas) telephoned the Dallas County sheriff's office to notify the city that a tornado had "come down" in Duncanville. The message was relayed to the city police by a direct line between the sheriff's office and the police dispatcher's board. On the receipt of this message from Duncanville, the police dispatcher warned police patrol cars in the southwestern area of Dallas to be on the alert for an approaching tornado.

The police in patrol cars in the southwestern area soon saw the tornado and radioed the police dispatcher that there was a tornado "on the ground" progressing toward Dallas. The local news agencies and the television stations monitor the police circuit, and it was by this means that the radio broadcasting cars were alerted and sent to the scene of the tornado path. At about 4:10 p. m. telephone calls using the "hot lines" to Parkland Hospital and to the ambulance centers at the funeral homes were used to notify these agencies of the possibility of many casualties.

It was possible for police patrol cars to withdraw from the area threatened by the tornado, to follow along with it, and to come back into the devastated area behind the storm. It was even possible for a mobile broadcasting car from one of the local radio stations to follow along close to the path of the tornado as it actually progressed. The broadcaster gave a running account of the progress of the tornado cone, and, in this way, many people of the city heard a minute-to-minute description of it. Numerous photographs were taken of this storm during its various stages; moving pictures obtained by several photographers have been put together into a full length film lasting more than half an hour. This film has been made available by one of the local television stations. The statement that this is the "best documented tornado on record" is probably justified for, in addition to the observations previously recounted, it is estimated that up to 100,000 persons watched the tornado's journey across the western portion of their city from the windows of the downtown business buildings or their homes.

After the police cars re-entered the disaster zone, they remained in radio contact with the police dispatcher and reported the progress of rescue activities. To prevent confusion an attempt was made to establish radio discipline by asking patrol cars to call in only under circumstances of extreme emergency. The police dispatcher believes that radio traffic did not fall far behind the requirement of the messages waiting. The dispatching room held a number of routine messages off the air until the disaster situation was under control.

Rescue Operation.—The Dallas city police are accustomed to handling heavy traffic conditions in the vicinity of the Cotton Bowl football field by a system described as "the command post" system. At the time of Cotton Bowl traffic problems, each "command post" is set up for control of traffic at a strategic intersection. A "command post" consists of a patrol car or motorcycle with radio communication to the dispatcher and any auxiliary vehicles which may be assigned to this point. Information is fed by radio to the central dispatcher, and orders are returned to the "command posts." Thus, control of traffic is made flexible in accordance with the demands of the existing situation.

A similar arrangement was used at the time of the tornado. A total of 10 "command posts" were established along the 16-mile track of the tornado, but all of the posts were not operating at once. They were moved in leap-frog fashion along the route of the storm as the rescue work progressed so that three to five posts were operating at any one time. These posts functioned chiefly for the control of traffic and cleared all activities through the central dispatcher. The police in the disaster zone did not participate actively in rescue operations to any great extent but served as control points for the rescue workers.

The ambulances were ordered by the police dispatcher to report to specific "command posts" and to take their directions from a patrol car at that post in order to pick up the casualties. The dispatcher designated the "command post" in accordance with requests for ambulances which came from the patrol cars or through telephone communications direct from the public. The official ambulances were instructed to take casualties to Parkland Memorial Hospital. Some ambulances not equipped with radios were in operation on the night of the disaster; these were always sent out in company with a radio-equipped ambulance.

The Dallas Emergency Corps and at least three of the emergency squads sponsored by commercial enterprises were called by the police dispatcher through direct telephone communications. Several of these rescue squads went into action in the immediate disaster zone in cooperation with the "command posts" which controlled traffic entering and leaving the disaster area.

The rescue operation seems to have been under the direct control of the police dispatcher with the supervision of the chief of police. It functioned so smoothly that by 7 p. m. the dispatcher had ordered all ambulances back to their stations. The largest problem encountered by the police during the day of the disaster was to establish traffic control along the main highways leading from the disaster areas to the hospitals since it was hard to exclude sightseers who insisted on passing police blockades.

Parkland Functions in the Emergency.—About 4:10 p. m. Parkland Memorial Hospital was notified by direct telephone call from the police dispatcher's office that a large number of casualties should be expected. The hospital alerted its house staff. It was fortunate that a number of the staff surgeons were still in the hospital because of an unusual "heart operation" being done that afternoon; these men were available for immediate duty. Also available were approximately 120 medical students attending classes in the school and about 175 student nurses. Therefore, there was no shortage of hospital personnel.

The administrator was in the hospital when the notification was received. He started action at once, with the available staff. The telephone operators on duty called the staff members who were designated by the disaster-control plan to be called for a minor disaster. About one hour later additional personnel from among those listed to be called in case of a major disaster were summoned.

The first staff doctor to reach the receiving area was the surgeon designated by the disaster-control plan of the hospital as director of activities of the professional staff.[2] He had seen the approach of the tornado from his own office, which was in an adjacent medical building. He hurried from his office to the hospital and was on duty before the first patients arrived. The surgeon designated as second-in-command was already in the hospital. From the unfinished tenth floor of the hospital he watched the tornado move across the Trinity river. After the storm had passed he went to the emergency ward where residents were already working on the first five patients. He assumed the supervision of triage from the first surgeon and served throughout the rest of the night as triage officer, supervising the work of the residents.

At the initial screening by the triage officer, all seriously injured patients or those who were possibly seriously injured were sent into the emergency ward for evaluation and treatment by the residents. Children with minor injuries were sent to the pediatric ward from which all of the patients usually present were evacuated. Adults with minor injuries were sent to the waiting rooms for observation.

The surgeon in charge of the professional activities directed those who reported for duty to various areas to carry out their work, and he assigned patients to appropriate divisions of the hospital. For this purpose he was in constant communication with the administrator, who gave him information derived from the police. The administrator was in frequent contact by police telephone with the police dispatcher. Casualty lists were issued at intervals in cooperation with police officers waiting in the police room in the emergency ward. The physician vice-chairman of the Civil Defense and Disaster Commission came to the emergency ward of Parkland early in the evening and participated in the over-all direction of activities. He was in frequent contact with Civil Defense Headquarters.

The few emergency cases requiring immediate surgery were sent up by way of an express elevator from the emergency ward to the operating room. Those requiring x-rays were sent to that section of the x-ray department immediately adjacent to the emergency ward. Five teams to manage the suturing of minor wounds were set up in adjacent laboratory space. The triage officer was in complete charge of these activities and assigned specific physicians to specific patients.

The chief surgeon of Parkland Memorial Hospital drove from his home and followed an ambulance up the left lane of one of the major boulevards to reach the hospital. He went at once to the operating room where he assumed full charge of the activities in that area. He made the necessary policy decisions concerning therapy and gave advice to the surgeons who were carrying out the procedures. About 12 major operations were performed in the operating room. As many as four were going on at one time, but, of these, several were minor. There were two patients with head injuries requiring craniotomies; four or five patients with open long-bone fractures were operated upon that night; also, two or three patients with major lacerations were handled by débridement and preparation for delayed closure.

The staff men interviewed were of the opinion that their greatest need was for better intrahospital communication. During the night of the disaster they used student nurses as runners but found that this system did not function quickly or accurately enough.

A second criticism offered by the staff surgeons was that there was no method for re-sorting the patients who were referred for x-rays after the first triage. Apparently, after the films were taken, there was not a rapid return of patients to the emergency ward, and several fairly serious developments occurred among the waiting patients. One child was discovered to have a fractured femur that was unsuspected. A woman was found to have serious intra-abdominal vascular laceration which subsequently caused her death.

It was not necessary to expand the activities of the emergency ward into nearby nurses' classrooms, nor was there need to admit patients to beds in the teaching and lecture areas which had been provided with facilities for patient care. These steps could have been taken if the situation had demanded them.

In addition to the 178 disaster casualties (of whom 41 were admitted), about 175 ordinary emergency cases were treated that day in the emergency ward of Parkland Memorial Hospital. A duplicate tag system was used for the disaster casualties who were admitted to the hospital. The tags were not available for study. Very little record was kept of the ambulatory patients who were discharged after treatment.

By 6:45 p. m. the last of the casualties were admitted. Prior to 11 p. m. almost all of the major activity of an emergency nature had been completed.

Only two of the patients who reached Parkland Memorial Hospital alive died. One was the woman who had massive intra-abdominal hemorrhage from multiple injuries to major vessels. The other was an infant. No patients developed clostridial infections, and the surgical staff reported only one instance of major sepsis in the hospitalized patients. Little is known of the incidence of sepsis among the patients who were treated and discharged the same night.

It was generally agreed that, on the night of the tornado, Parkland Hospital was not taxed beyond its capacity to handle patients. About 6 or 7 p. m. that evening the surgeon-in-charge and the administrator discussed the possibility of diverting patients to other hospitals. They reached the decision not to do this because: 1. They concluded from police sources that the anticipated casualty load could be handled by Parkland. 2. Parkland was well equipped to accept charity patients whereas the handling of charity patients at other hospitals might create a difficult financial and administrative problem to be settled in the future. 3. The emergency activity at Parkland was good experience for the staff. The physician vice-chairman of the Civil Defense and Disaster Commission was aware of this decision and concurred in it.

Although it was never necessary to activate the plan to divert casualties to other hospitals, a few disaster victims were taken directly to other Dallas hospitals. None of these hospitals were notified of the tornado directly by the police, but most received notice of the passage of the tornado by staff members who saw it. Personnel were called together to "stand by" and to await any activity. Only one of these hospitals received more than one or two disaster casualties during the night. Methodist Hospital, situated on the west side of the Trinity river, received most of its emergency cases from the residential section located in southwest Dallas. Because of the recognized position of Parkland as the "emergency" hospital and the existence of high-speed trunk highways leading there, most of the patients from the west side of the river were taken to Parkland, although in certain instances Methodist Hospital may have been nearly as close. Methodist Hospital actually received 18 patients during the night of the storm. Of these 18 patients, 1 was dead on arrival; 6 were admitted to the hospital; and 11 were treated and discharged.

Summary and Appraisal

The medical care rendered to the casualties of the disaster in Dallas was of a high order. There were a number of circumstances which made this possible. Some of these were circumstances inherent in the nature of the tornado itself; some were the result of careful and intelligent planning for the "emergency functions" of the Parkland Memorial Hospital; and others were the result of preexisting arrangements in the functioning of the city which made possible closely controlled cooperation between the activities of the police department and the rescue services. All these considerations had important influences on the favorable operation of the medical care services; however, the planning of the Parkland Hospital and the smoothly operating rescue system were most vital to success.

The keen interest in planning for emergency medical service shown in Dallas was responsible for the creation of a hospital built to provide care in case of disaster. Its physical plant is arranged so that, when the necessity arises, the function of treating emergencies may be expanded easily from the normal space into thoughtfully arranged adjacent areas. The internal operation of Parkland's disaster-control plan seemed to be very effective, and, since it was never necessary to expand the space assigned to emergency functions to the planned maximum, it seems likely that an even larger volume of patients could have been handled well. There was no opportunity to test the plan for diversion of patients to other hospitals when Parkland was functioning at capacity.

Since the hospital was planned for the treatment of casualties in case of disaster and established as the hospital where most emergency cases and indignent patients are treated, the police, the ambulance drivers, and injured persons themselves were oriented toward the use of Parkland when disaster struck. This orientation contributed much to the success of the rescue operation; yet, the long established cooperative relationship between the police department and the ambulance services seems to have been the most important factor in the smooth operation of the rescue and transportation of casualties. The police dispatcher had direct control over the abundant official ambulances. The standard practice of the police department was to establish "command posts" around the periphery of a congested traffic area for supervision of traffic. Similar "command posts" were set up to direct the flow of traffic along the path of the tornado. It is clear that this organized system contributed greatly to the control of traffic in the immediate area of the impact zone itself. Less adequate supervision of traffic was in evidence along the highways leading from the disaster zone to the hospitals.

The limited nature of the problem presented to the medical authorities here as compared with the problems presented by certain larger natural disasters which occurred elsewhere in the past left untested some of the administrative concepts and physical arrangements in disaster-control planning for the area, but this fact does not detract from the important successes of the whole operation. These successes and the lessons learned may be translated into plans suitable for Dallas, Texas, in the future or may be profitably utilized in the formulation of such plans for other cities.

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MEDICINE AND THE LAW

REAPPRAISAL OF EUGENIC STERILIZATION LAWS

It is often observed that the law is painfully slow in its acceptance of scientific progress. However, in one area, eugenic sterilization, the law has moved with such rapidity that today many persons question whether this swift acceptance was wise from either a scientific or a legal point of view.

Although in 1895 the word "eugenics" as it is used today was completely unknown, by 1917, 15 states had adopted eugenic sterilization laws, and at the end of another 20-year period a total of 32 states had enacted such legislation. An examination of all the factors responsible for this rapid growth would encompass many economic and political factors which are beyond the scope of this study, but there is no doubt that three events which occurred at the end of the 19th century played a most important part in the adoption of legislation authorizing compulsory sterilization. They were the launching of the eugenics movement by Sir Francis Galton, the rediscovery of Mendel's laws of heredity, and the development of simple, nondangerous surgical techniques for the prevention of procreation.

The term "eugenics" is derived from a Greek word meaning "well born." In 1883 Sir Francis Galton coined the word and defined it as the study of agencies under social control that may improve or impair future generations either physically or mentally.[1] In 1904 he officially launched the eugenics movement, which had a twofold aim: (1) positive eugenics—encouragement of the propagation of the biologically fit—and (2) negative eugenics—discouragement of the reproduction of inferior stock. During this same period, the laws of heredity formulated by the Austrian monk, Gregor Mendel, forgotten since their publication 40 years earlier, were rediscovered. Although Mendel's work had been confined to plant life, it was seized on as being applicable to human beings. The proponents of this view decided that mental illness, mental deficiency, epilepsy, criminality, pauperism, and various other defects were hereditary. There was considerable agitation for corrective action, based on the premise that these conditions were hereditary. Since attempts at cure were considered futile for hereditary defects, preventive measures appeared to be the only way to eliminate these conditions.

A few years prior to the rediscovery of Mendel's laws, Dr. Harry C. Sharp of the Indiana State Reformatory developed a method of sterilizing men (vasectomy)[2] and at about the same time the now standard method of sterilizing women (salpingectomy) was discovered in France.[3] Neither of these procedures is hazardous under modern surgical conditions, nor do they materially lower sexual powers.[4]

The first sterilization law was passed only three years after Galton started the eugenic movement, and, as mentioned earlier, this legislation was soon followed by statutes in many other states. In 1927 the United States Supreme Court upheld the Virginia sterilization law[5] and 10 years later Georgia[6] became the 32nd and to date the last state to adopt this type of legislation.

It might be assumed from this acceptance by the state legislatures and the Supreme Court that the status of eugenic sterilization is well settled in the United States. However, there is still considerable controversy concerning these laws. Several scientific studies undertaken during the last 25 years disagree with the conclusions of the eugenicists. In addition, the laws are often attacked on constitutional, moral, social, and theological grounds.[7] In view of this conflict a reappraisal of sterilization laws appears necessary, especially since they involve the very important right of procreation.

The reappraisal of sterilization laws undertaken by this study will be limited to the effect of these laws on the mentally ill and the mentally deficient. Although in many states the laws are applicable to other groups such as epileptics, "hereditary criminals," and sex deviates, 95% of all reported sterilizations have been performed on mentally ill or mentally deficient persons. Although many persons believe that most sterilizations are performed on the mentally deficient, as of Jan. 1, 1960, a total of 27,436 mentally ill persons and 31,931 mentally deficient persons had been sterilized.[8]

Historical Background

Some of the proponents of eugenic sterilization were so zealous that they began sterilizing people before there was legislative authorization for the procedure. In the middle of the 1890's, F. Hoyt Pilcher, superintendent of the Winfield, Kansas, State Home for the Feebleminded, castrated 44 boys and 14 girls. Public sentiment is considered responsible for the ending of this activity.[9] Dr. Martin W. Barr, superintendent of the Pennsylvania State Training School, claimed that he performed the first sexual sterilization to prevent procreation in 1889. Three years later, when he was president of what is now known as the American Association on

Mental Deficiency, he reported the operation and asked, "What state will be the first to legalize this procedure?" [10] Another impatient eugenicist was Dr. Harry C. Sharp, who devised the surgical operation known as vasectomy. He reportedly sterilized 600 or 700 boys at the Indiana reformatory before the adoption of the Indiana Act. [11] It is also claimed that superintendents of institutions in several states were secretly sterilizing feebleminded persons.[12]

The legislative history of eugenic sterilization began in 1897, when a bill authorizing such operations was introduced in the Michigan legislature.[13] This bill was defeated and it was Pennsylvania, eight years later, which became the first state to pass a sterilization bill. It was entitled an "Act for the Prevention of Idiocy" and required that "each and every institution . . . entrusted . . . with the care of idiots and imbecile children to appoint a neurologist and a surgeon . . . to examine the mental and physical condition of the inmates." [14] If, in their opinion, procreation was inadvisable, and there was no probability of improvement of the mental condition of the inmate, the surgeon was authorized "to perform such operation for the prevention of procreation as shall be decided safest and most effective." Governor Pennypacker refused to sign the bill and returned it to the Senate with the following message.

> This bill, has what may be called with propriety an attractive title. If idiocy could be prevented by an Act of Assembly, we may be quite sure that such an act would have long been passed and approved in this state. . . . What is the nature of the operation is not described, but it is such an operation as they shall decide to be "safest and most effective." It is plain that the safest and most effective method of preventing procreation would be to cut the heads off the inmates, and such authority is given by the bill to this staff of scientific experts. . . . The bill is, furthermore, illogical in its thought. . . . A great objection is that the bill . . . would be the beginning of experimentation upon living human beings, leading logically to results which can readily be forecasted. The chief physician . . . has candidly told us, . . . that "Studies in heredity tend to emphasize the wisdom of those ancient peoples who taught that the healthful development of the individual and the elimination of the weakling was the truest patriotism—springing from an abiding sense of the fulfillment of a duty to the state." . . . .[15]

Although many sterilization bills have been introduced in Pennsylvania subsequent to this veto, none has succeeded in becoming law.

It was Indiana which finally enacted the first sterilization law in 1907, two years after Pennsylvania's first attempt.[16] However, the Indiana statute was eventually declared unconstitutional [17] as were all other similar laws which came before the courts prior to 1925.[18]

The statistics concerning sterilization during this early period are quite interesting. As of Jan. 1, 1921, the states reported a total of 3,233 sterilizations performed since 1907, the beginning of legalized operations.[19] If we add the known unauthorized operations in Kansas and Indiana the total of sterilizations up to 1921 is about 3,900. More than 20% of these operations were executed either without any statutory authority or under statutes which were subsequently declared unconstitutional.[20] The balance of the sterilizations took place under laws whose constitutionality had never been tested. It is also noteworthy that, although many people believed that sterilization is usually recommended for the mentally deficient rather than the mentally ill,[21] more than 80% of the sterilizations reported in 1921 were performed on mentally ill persons.[22]

Precedent of *Buck* v. *Bell*

The advocates of eugenic sterilization achieved a substantial victory in 1925, when the courts of two states held their sterilization laws valid. The first decision was rendered on June 18, 1925, by the Supreme Court of Michigan in the case of *Smith* v. *Command*.[23] A few months later on Nov. 12, 1925, in the case of *Buck* v. *Bell*,[24] the Supreme Court of Appeals of Virginia held a sterilization statute to be a valid enactment under the state and federal constitutions. An appeal was taken from this decision to the United States Supreme Court. In a brief opinion which is probably best remembered for Mr. Justice Holmes' comment, "Three generations of imbeciles are enough," the court held [25] that the law in question was a reasonable regulation under the police power of that state and did not violate either the due process or the equal protection clause of the 14th amendment.

Carrie Buck, the plaintiff in the case, was an 18-year-old woman committed to the Virginia State Colony for Epileptics and Feebleminded. She was the daughter of a feebleminded mother and the mother of an illegitimate, feebleminded child. The Virginia court found that Carrie Buck was "the probable potential parent of socially inadequate offspring likewise afflicted." [26]

No objection was made to the procedural provisions of Virginia law. Instead the attack was made on the substantive law, the contention being that the sterilization order could not be justified on the existing grounds. Justice Holmes, speaking for the court, made the following statement.

> We have seen more than once that the public welfare may call upon the best citizens for their lives. It would be strange if it could not call upon those who already sap the strength of the state for these lesser sacrifices, often not felt to be such by those concerned, in order to prevent our being swamped with incompetence. It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes. . . . Three generations of imbeciles are enough.[27]

This decision was followed by an abundance of eugenic sterilization legislation. Twenty statutes were passed in the ensuing 10 years,[28] most of them closely patterned after the Virginia law. Only nine cases [29] have been found involving the validity of sterilization laws applicable to the mentally ill and the mentally deficient since *Buck* v. *Bell.* Three of these laws[30] were declared unconstitutional, but they were based on procedural deficiencies rather than the substantive issues determined in *Buck* v. *Bell.* In the six cases in which the laws were upheld, five[31] rely on the decision in *Buck* v. *Bell* and the sixth was concerned with the adequacy of the law's procedural provisions.[32]

The only sterilization law considered by the United States Supreme Court subsequent to *Buck* v. *Bell* was an Oklahoma statute which provided for the sterilization of habitual criminals.[33] The court held the law unconstitutional on the grounds that its exception of "persons convicted of offenses arising out of violation of the prohibitory laws, revenue acts, embezzlement, or political offenses" violated the constitutional prohibition against class legislation. Although this case did not consider the same issues as *Buck* v. *Bell* some legal scholars have suggested that Justice Jackson's concurring opinion might be interpreted as casting doubt on the validity of all sterilization laws.[34] Critics of the *Buck* v. *Bell* decision have also speculated on the possibility of a reversal of opinion by the Supreme Court if a question is raised with respect to another eugenic sterilization law.[35] The reasons for this view and criticisms of *Buck* v. *Bell* will be discussed in the subsequent section on current views on sterilization legislation.

Analysis of Current Statutes

At present 28[36] states have eugenic sterilization laws, in 26 of which they are compulsory.[37] Mentally deficient persons are subject to the laws in all of these states and in all but two they are also applicable to the mentally ill.[38] Seventeen states[39] include epileptics in the groups designated by such laws.[40] Nineteen of these laws apply to persons confined in hospitals or other institutions caring for afflicted persons with the named conditions, while the remaining laws include persons who are not confined.[41]

The involuntary procedure is usually commenced by an application from the superintendent of the institution to a designated administrative agency which has the authority to grant a sterilization order. Although most of the states now require notice, a hearing, and judicial appeal, there are five states which do not require a hearing and four that make no provision for judicial appeal.[42] The majority view of the few state supreme courts which have considered the procedural provisions of sterilization laws is that the patient must be given notice and accorded a hearing or else be allowed to appeal the sterilization order to a court.[43] Although a California district court of appeals came to a contrary decision,[44] the California sterilization law was subsequently amended in 1951 and now provides for both notice and judicial appeal.[45] The usual ground for issuing the sterilization order is that "according to the laws of heredity, the person is the probable potential parent of socially inadequate offspring likewise afflicted."[46]

On only 23 occasions have cases involving the sterilization of inmates of state institutions come before the courts.[47] According to the Human Betterment Association, one would expect to find the curtailment of rights in an area as important as procreation strongly contested. They conclude that the dearth of cases "speaks well not only of the care and forethought state legislators have given to the consideration of the provisions of the laws but also of the care exercised in their application by administrators."[48] However, an examination of the sterilization picture in Alabama casts considerable doubt on the validity of this conclusion.

Alabama has had a sterilization law since 1928 which merely says that the Assistant Superintendent of the Institution for Mental Defectives may have patients sterilized after consultation with the Superintendent.[49] There are no provisions for notice, a hearing, or judicial appeal. The statute has the same procedural deficiencies as the 1928 law.

Although this bill has not been amended since 1928, in 1935 the Alabama legislature passed a law which would have added the mentally ill and certain sexual offenders to the groups of persons subject to sterilization.

On June 10, 1935, the Governor of Alabama asked the justices of the Supreme Court of the state for an advisory opinion as to whether the bill was a valid exercise of the police power of the state.

The court concluded that the law would be unconstitutional on the grounds that the sterilization of a person cannot be effected without a hearing on notice before a duly constituted tribunal or board, and if this be not a court, then with the right of appeal to a court for judicial review of the findings of the board.[50] The governor consequently vetoed the bill.

According to several articles on sterilization laws, this decision cast such doubt on the validity of the existing Alabama law that it has not been used since 1935.[51] However, in 1951, a legislative committee investigating the state hospitals stated that 224 patients had been sterilized since the 1935 decision. The committee was of the opinion that the Alabama law was unconstitutional because of the advisory opinion and deplored the fact the above-mentioned patients had been denied their constitutional rights. It strongly recommended that the law be repealed and that the superintendent of the Institution for the Mentally Deficient be instructed not to perform any more operations pending repeal of the law.[52] Although it is not known whether this latter instruction was carried-out, the law has not been repealed.

It is not reasonable to assume, at least in the case of Alabama, that the lack of cases attacking sterilization laws stems from the excellence of the law or the wisdom of the administrators in its application.

It is possible that the lack of cases is due to the inability of the mentally ill or mentally deficient person to handle his defense. For that matter, it is possible that he does not even understand the nature of the action. In most proceedings affecting personal or property rights, it is taken for granted that the parties are represented by attorneys. In a case in which they cannot afford legal representation, it is usually provided by a legal aid society, a public defender, or a court-appointed counsel who receives compensation from the state. It will be noted from the table that very few states provide for court-appointed counsel in sterilization proceedings. It is impossible to estimate what effect this policy may have had on the status of sterilization legislation. For example, it has been asserted that the suit in *Buck* v. *Bell* was a friendly one selected by the superintendent of the State Colony for Epileptics and Feebleminded to be used as a test case.[53] Carrie's guardian is alleged to have been appointed by the state, not the county, and to have been paid $25 for the entire case, which averaged out to $1.00 a month.[54]

Current Views on Sterilization Legislation

Scientific View.—The American Neurological Association's Committee for the Investigation of Eugenical Sterilization summarized the main arguments of the proponents of sterilization as follows. 1. Mental illness, mental deficiency, epilepsy, pauperism, and certain forms of criminality are steadily increasing. 2. Persons with these diseases propagate at a greater rate than the normal population. 3. These conditions are hereditary. 4. Environment is of less importance than germ plasm in the creation of these conditions. Implicit and sometimes explicit in this point of view is that euthenics [55] is against natural selection because it keeps alive the unfit and, therefore, is against the racial welfare.

Although it was accepted by the state legislatures and the courts that at least the inheritability of these conditions had been scientifically proved, studies undertaken in the last 25 years have thrown substantial doubt on this conclusion.[56] The most important of these studies was that conducted by the American Neurological Association, which made the following answers to the statements of the advocates of eugenic sterilization laws.

> [1.] There is nothing to indicate that mental disease and mental defect are increasing, and from this standpoint there is no evidence of a biological deterioration of the race.[57] [2.] The reputedly high fecundity of the mentally defective groups . . . is a myth based on the assumption that those who are low in the cultural scale are also mentally and biologically defective.[58] [3.] Any law concerning sterilization . . . under the present state of knowledge [of heredity] should be voluntary . . . rather than compulsory.[59] [4.] Nothing in the acceptance of heredity as a factor in the genesis of any condition considered by this report excludes the environmental agencies of life as equally potent, and in many instances as even more effective.[60]

Concerning the claim of eugenicists that the efforts of society to help the unfit works against the welfare of the race the committee offered a counterclaim.

> It is precisely in those communities where social care is good that we find the evidence of the finest culture and, on the whole, the best biology. It is in those communities where social care is poor that the population presents an appalling spectacle of degradation.[61]

One year later the American Medical Association's Committee to Study Contraceptive Practices and Related Problems reported as follows.

> Our present knowledge regarding human heredity is so limited that there appears to be very little scientific basis to justify limitation of conception for eugenic reasons. . . . There is conflicting evidence regarding the transmissability of epilepsy and mental disorders.[62]

A recent opinion to the same effect is that expressed by the Mental Health Committee of the South Dakota Medical Association in the "Explanation of the Proposed South Dakota Mental Health Act."

> Medical science has by no means established that heredity is a factor in the development of mental disease with the possible exception of a very few and rare disorders. The committee holds that the decision to sterilize for whatever reason, should be left up to the free decision reached by patient and family physician mutually and that the State has no good reason to trespass in this area.[63]

There appears to be little doubt that there is a conflict of opinion over the inheritability of the conditions covered by eugenic sterilization laws. This conflict is important because the legislatures and the courts have assumed to date that the conditions are hereditary.

Legal View.—There are two legal viewpoints concerning the constitutionality of compulsory sterilization laws. The first theory which became prominent was that the constitutionality of sterilization statutes depends on their scientific validity. Many proponents of this view believe that the scientific premises on which the statutes rest are erroneous and that, consequently, compulsory sterilization is an arbitrary and unreasonable deprivation of liberty.[64]

The second theory considers the right of procreation as a fundamental liberty and one which cannot be interfered with by a government order.[65] The analogies used by Justice Holmes to uphold this type of legislation have been severely criticized by some of the proponents of this view. Justice Holmes said, "The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes." [66] However, when the Massachusetts Supreme Court upheld the vaccination law, it offered this argument.

> If a person should deem it important that vaccination should not be performed in his case, and the authorities should think otherwise, it is not in their power to vaccinate him by force, and the worst that could happen to him under the statute would be the payment of the penalty of five dollars.[67]

Thus, it has been argued that the vaccination and sterilization laws are not analogous, because "so far as concerns liberty, there would appear to be a real difference between assessing a fine and compelling submission." [68]

Justice Holmes also believed that if the nation could call on its best citizens to sacrifice their lives in time of war, it should be able to "call upon those who already sap the strength of the state" to make a lesser sacrifice. This analogy has been contested on the ground that there is a necessity and an urgency that causes us to sacrifice men in self-defense which is wholly lacking in the case of eugenic sterilization.[69]

The fear has also been expressed that the logic of the decision in *Buck* v. *Bell* might be extended beyond its present limited boundaries.

> There are other things besides physical or mental disease that may render persons undesirable citizens or might do so in the opinion of a majority of a prevailing legislature. Racial differences for instance, might afford a basis for such an opinion in communities where the question is unfortunately a permanent and paranoid issue.[70]

In view of suggestions made by some eugenicists, the fear that the scope of eugenic sterilization laws may be expanded is not irrational. A Model Eugenical Sterilization Law proposed that the following persons be subject to sterilization: "(1) Feeble-minded; (2) Insane (including the psychopathic); (3) Criminalistic (including the delinquent and wayward); (4) Epileptic; (5) Inebriate (including drug-habitués); (6) Diseased (including the tuberculous, the syphilitic, the leprous, and others with chronic, infectious and legally segregable diseases); (7) Blind (including those with seriously impaired vision); (8) Deaf (including those with seriously impaired hearing); (9) Deformed (including the crippled); and (10) Dependent (including orphans, ne'er-do-wells, the homeless, tramps and paupers)." [71]

This model law also recommended the sterilization of persons who do not exhibit any of the above traits, if the laws of heredity indicate that one-fourth of their potential offspring may show such traits. It also advocated sterilization if one-half of the potential offspring might carry genes for such qualities, even if the offspring will not be a socially inadequate person.[72]

In recent years there have also been proposals for sterilization on an environmental basis.[73] It has been alleged that existing laws would need few, if any, changes in wording to provide for such procedures.[74]

A discussion of the merits and defects of environmental sterilization is outside the scope of this paper. However, with regard to the constitutionality of such laws, it appears that if the courts should decide that the state has no right to invade the bodily integrity of an innocent person who has committed no crime, this decision would probably apply to both eugenic and environmental sterilization laws.

Conclusions

Since sterilization is a drastic remedy and generally a permanent infringement of bodily integrity, those affected by laws authorizing it are entitled to every reasonable precaution. Thus far they have not been adequately protected. The sterilization of persons (*a*) without legal authorization, (*b*) before the constitutionality of the laws is tested, (*c*) under unconstitutional laws, and (*d*) with lack of representation by counsel are all clear illustrations of this disregard of rights.

The fact that scientific opinion differs as to the value of sterilization certainly indicates that the merits of this type of legislation should be reevaluated. Since court decisions have assumed that the conditions included in sterilization statutes are hereditary, the constitutionality of such statutes is questionable if scientific opinion is divided concerning the effectiveness of this procedure. A study of sterilization statistics indicates that its use is steadily decreasing. However, it is not known whether this stems from doubts concerning the constitutionality of the laws, public reaction, or a change in medical opinion.

In recent years it has been questioned whether sterilization is constitutional even if scientific studies could demonstrate its effectiveness in reducing mental disability. In fact, it has been suggested that in the near future "three generations of imbeciles may no longer be the prediction and even where it is, it may no longer be enough" and that "*Buck* v. *Bell* may in the end serve as a monument only to the wit but not the wisdom of Mr. Justice Holmes." [75]

APPENDIX.—*Criteria for Determining Applicability of Involuntary Sterilization Laws*

		Condition		
Summary of Specifications	State	Mental Illness	Mental Deficiency	Epilepsy
According to laws of heredity, person is probable potential parent of socially inadequate offspring likewise afflicted				
	Arizona	X	X	X
	Mississippi	X	X	X
	New Hampshire	X	X	X
	Oklahoma	X	X	X
	South Carolina	X	X	X
	Utah	X	X	X
	Virginia	X	X	X
	West Virginia	X	X	X
Procreation would produce children with an inherent tendency to named conditions, i. e., mental illness;				

	State	Condition		
		Mental Illness	Mental Deficiency	Epilepsy
or physical or mental condition of patient would be improved by sterilization				
	Connecticut	X	X	
	Georgia	X	X	
	Idaho	X	X	X
	Iowa	X	X	
	Kansas	X	X	X
	Maine	X	X	
	Michigan	X	X	X
	North Dakota	X	X	X
	Oregon	X	X	X
Procreation deemed inadvisable				
	Delaware	X	X	X
	Wisconsin	X	X	
Person afflicted with mental disease which may have been inherited and is likely to be transmitted to descendants; mental deficiency; or marked departures from normal mentality				
	California	X	X	
	South Dakota	X	X	
When deemed advisable				
	Alabama		X	
Person afflicted with hereditary forms of insanity that are recurrent; epilepsy; or primary or secondary types of feeblemindedness				
	Indiana	X	X	X
Idiot or feebleminded or insane person who is treated, trained, or cared for within a custodial institution				
	Montana	X	X	X
Mentally deficient patients eligible for parole or discharge				
	Nebraska		X	
If considered in the best interest of mental, moral, or physical improvement of patient, or for public good				
	North Carolina	X	X	X

A general bibliography, a complete list of references, statutory citations and tables describing procedural requirements for sterilization, and statistics on the use of sterilization may be obtained on request from the Legal and Socio-Economic Division.

GOVERNMENT SERVICES

PUBLIC HEALTH SERVICE—"TREATING CANCER"

Various treatments of malignant diseases are explained in terms readily understandable to the layman, in a new booklet. Single copies may be obtained from the Public Health Service. Larger quantities may be purchased from the Superintendent of Documents, Washington 25, D. C.

Joint Meeting on Poliomyelitis.—A joint Russian-United States report on the poliomyelitis meeting held in Moscow in May was made by Dr. David E. Price, assistant surgeon general of the Public Health Service and chief of the United States delegation. The meeting was attended by 13 United States and 15 Russian physicians and was concerned chiefly with technical discussions of research, production, and testing of live poliomyelitis vaccines. The Russians reported successful use of the live virus vaccine which was developed by Dr. Albert Sabin, director of research at Children's Hospital, Cincinnati. Pieces of candy containing Russian-produced Sabin vaccine have been given to 60 million Russians, from the ages of 2 months to 20 years, with encouraging results.

The Americans described field trials of live virus vaccines which were developed by Dr. Herald Cox of Lederle Laboratories, Dr. Hilary Koprowski of the Wistar Institute, and Dr. Sabin. It was agreed that further exchange of information and comparative studies is desirable and that such information should be furnished to the World Health Organization with a view to the ultimate development of international recommendations. Use of live virus vaccines in the United States at present is limited to carefully controlled field studies. No data presented at the Moscow meeting would justify changing this policy.

In addition to Drs. Price, Sabin, and Koprowski, the Americans who attended the Moscow meeting were: Dr. M. Benyesh-Melnick and Dr. Joseph E. Melnick, Baylor University School of Medicine, Houston, Texas; Dr. Theodore Boyd, National Foundation, New York; Dr. Victor Cabasso, Lederle Laboratories, Pearl River, N. Y.; Dr. Eugene Flipse, University of Miami School of Medicine, Miami, Fla.; Dr. John P. Fox, Institute for Public Health Research, New York; Dr. Thomas Francis, University of Michigan, Ann Arbor, Mich.; Dr. Herman Kleinman, Minnesota Health Department, Minneapolis, Minn.; Dr. Alexander Langmuir, Communicable Disease Center of the Public Health Service, Atlanta, Ga.; and Dr. Roderick Murray, National Institutes of Health of the Public Health Service, Bethesda, Md.

MEDICAL NEWS

DISTRICT OF COLUMBIA

Health Award Recipients Named.—Dr. Donald H. Stubbs, chairman of the board, National Association of Blue Shield Plans, was named one of three national civic leaders to receive the 1960 "Health-USA" award sponsored jointly by the Metropolitan Washington (D. C.) Board of Trade and the Medical Society of the District of Columbia. Dr. Stubbs was selected for ". . . his distinguished contributions to the health of the American people." The two other recipients of the "Health-USA" awards, which are given annually to recognize "Statesmanship in Health," are Major Gen. Howard McC. Snyder, physician to the President of the United States, and Mr. Elmer H. Bobst, chairman of the board, Warner-Lambert Pharmaceutical Company. Dr. Stubbs is clinical professor of anesthesiology at George Washington University Medical School.

KENTUCKY

Faculty Promotions.—The board of trustees of the University of Louisville School of Medicine in Louisville on June 16 announced faculty promotions, and the following faculty members were advanced to full professors of surgery: Dr. David P. Hall, Dr. Alvin B. Ortner, and Dr. George B. Sanders.

MARYLAND

Symposium and Exhibit on Research Equipment.—The 10th annual Instrument Symposium and Research Equipment Exhibit will be held Oct. 4-7 at the National Institutes of Health, Bethesda, Md. Primary topics for discussion on the scientific program include fluorescence, infrared, activation analysis, ultracentrifuge, microscopy, and electrodes. Sponsors of the symposium are the Washington sections of the American Association of Clinical Chemists, American Chemical Society, Instrument Society of America, Society of American Bacteriologists, and Society for Experimental Biology and Medicine. For information, write Mr. James B. Davis, National Institutes of Health, Bethesda 14, Md., Executive Secretary.

MASSACHUSETTS

Faculty Retirements.—Two members of the Faculty of Medicine at Harvard University, Boston, will retire on Aug. 31 to become professors emeriti. Dr. Allan Macy Butler will become professor of pediatrics, emertus, and Dr. Felix George Fleischner will become clinical professor of radiology, emeritus. At the same time, Dr. Butler will retire as chief of the Children's Medical Service at the Massachusetts General Hospital, and Dr. Fleischner will retire as radiologist-in-chief at the Beth Israel Hospital.

MICHIGAN

"Cell Bank" in Detroit.—Establishment of a "cell bank" to be used for research on cancer, viruses, and in general biology, was announced by Wayne State University College of Medicine and the Child Research Center of Michigan. The bank, one of three in the United States, will be directed by Cyril S. Stulberg, Ph.D., associate professor of microbiology, and Dr. Lawrence Berman, professor and acting chairman of the department of pathology, WSU College of Medicine. Living human and animal cells will be preserved by refrigeration. The formation of the three cell banks is the result of a new program initiated by the Viruses and Cancer Advisory Panel of the National Cancer Institute. Purpose of the study will be the proper classification and registry of human and animal cells grown in the laboratory. Currently, more than 100 different types of living cells are under cultivation in laboratories all over the world. New laboratories, to meet the special requirements of this project, have been constructed at both Detroit institutions. Funds were granted by the National Cancer Institute. The national Cell Culture Collection Coordinating Committee, of which Dr. Stulberg is a member, will assist researchers who grow tissues and cells for research purposes by promoting the study, proper classification, and registry of these forms of life. The American Type Culture Collection in Washington, D. C., will provide a national repository for standard strains.

NEBRASKA

Dr. Holyoke to Succeed to Dr. Latta.—Effective July 1, Dr. Edward A. Holyoke, professor of anatomy, will succeed John S. Latta, Ph.D., professor and chairman of the department of anatomy, University of Nebraska College of Medicine. Dr. Latta has been chairman of the department since 1941 and will continue as professor of anatomy.

Dr. Pfundt Named Department Chairman.—Dr. Theodore R. Pfundt is the new chairman of the department of pediatrics, Creighton University School of Medicine, Omaha. A graduate of the University of Oklahoma Medical School, he has served on that school's faculty and as a pediatric

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

consultant to the Oklahoma State Department of Health and associate director of the Oklahoma Poison Information Center. He joined the Louisiana State University medical faculty in 1958 and also served as senior pediatrician to the Child Development Program at Charity Hospital in New Orleans.

NEW JERSEY

Dr. McCormack Appointed Dean at Seton Hall.—The appointment of Dr. James E. McCormack, assistant vice-president of Presbyterian Hospital, New York City, as dean of the Seton Hall College of Medicine was announced June 13 by Rt. Rev. Msgr. John J. Dougherty, president of Seton Hall. Dr. McCormack succeeds the late Dr. Charles L. Brown, first dean of the school, who died last December. Dr. Hugh G. Grady, director of the department of pathology, has served as acting dean since that time. The new dean, a native of Jersey City, received his medical degree from New York University in 1939. From 1942 until 1950 he was associated with the New York University School of Medicine, starting as an assistant in medicine and serving from 1946 to 1950 as assistant dean. From 1948 to 1950 he was on leave of absence to serve as executive director of the Committee on Medical Sciences of the Research and Development Board of the Department of Defense. At the same time he served on the faculty of the George Washington University School of Medicine. From 1950 to 1951 he served as associate dean of the Post Graduate Medical School of New York University and the following year was appointed a professor of medicine and associate dean of the Post-Graduate School of the Columbia University College of Physicians and Surgeons. Dr. McCormack is chairman of the Licensure Committee of the American Association of Medical Colleges.

NEW YORK

Dr. Moe Becomes Research Director.—Dr. Gordon K. Moe, chairman, department of physiology, State University of New York Upstate Medical College, Syracuse, for 10 years resigned July 1 to become director of the Masonic Medical Research Laboratory on Bleeker Street, Utica. Dr. Moe will retain the title of research professor on the College of Medicine faculty in Syracuse. At Utica he will be in charge of research in the process of aging and in the study of specific diseases that the aged encounter. Dr. Moe is a member of the board of editors, American Physiology Society. Succeeding him as professor and chairman of the department of physiology is Dr. James B. Preston, assistant professor.

Dr. Hempelmann Named Department Head.—Dr. Louis H. Hempelmann Jr., professor of experimental radiology, University of Rochester School of Medicine and Dentistry, was appointed chairman of the department of radiology, effective July 1. Dr. Hempelmann succeeds Dr. George H. Ramsey, chairman of the department since 1948 and a member of the Medical School faculty since 1930, who retired June 30. Dr. Hempelmann, a member of the UR medical faculty since 1950, when he became associate professor of experimental radiology after two years at Harvard Medical School as a research associate in medicine, was promoted to full professor in 1951. He was on leave from 1943 to 1948 to serve as health division leader at Los Alamos, Scientific Laboratory of the Manhattan District, the first physician appointed there.

Conference for Indian Educators in Syracuse.—The Upstate Medical Center College of Medicine, Syracuse, was host to 40 Indian educators at a "Conference on Medical Education" June 15-18. The purpose of the conference was to give the Indian visitors "an over-all view of American medical education." They have been in the United States studying various specialties for the past year. Among the schools at which they have been studying are Harvard Medical School, Cornell University Medical College, University of Colorado School of Medicine, University of Pennsylvania School of Medicine, Johns Hopkins University School of Medicine, and Indiana University Medical Center. The conference was sponsored by the State University of New York College of Medicine, Public Health Division of the International Cooperative Administration, and the Rockefeller Foundation. This is the second Indian medical educators' conference to be held and the second time that Syracuse has been the host. Edward Dempsey, Ph.D., professor of anatomy, and dean of the College of Medicine at Washington University in St. Louis, gave the keynote address, "The Place of Basic Medical Sciences in Medical Education and Practice."

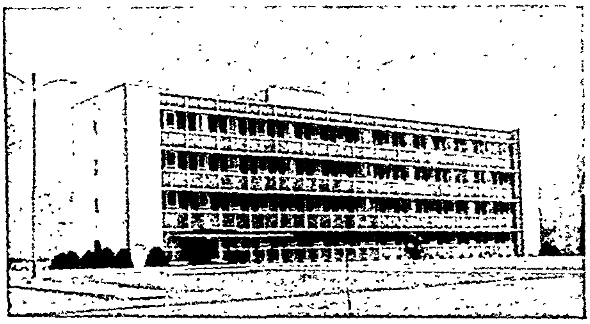
New York City

Alumni Election.—The alumni of the State University of New York Downstate Medical Center in Brooklyn elected Dr. Albert W. Cook as 1960-1961 president of the alumni association. He succeeds Dr. Abraham Jablons. Dr. Cook is head of the division of neurosurgery, department of surgery, at the Downstate Medical Center. Other officers of the association for 1960-1961 are: vice-president, Dr. Robert J. Hubbard; secretary, Dr. George Liberman; treasurer, Dr. Dennis J. Fiorentino; historian, Dr. Stanley D. Berliner; and associate historian, Dr. Walter J. O'Connor.

Test for Cancer of Cervix.—A $247,000, 14-month program to test for cervical cancer among women treated at Harlem and Metropolitan city hospitals was announced by the New York departments of health and hospitals. The Papanicolau smear test is to be given to from 50,000 to 75,000 women. Private physicians in Harlem will be asked to take similar tests of their patients. Harlem was chosen as the site of the program because of the high incidence of the disease there (8-20 per 1,000) as compared with the average city-wide rate (4-6 per 1,000). The project is being financed in part by a $99,800 grant from the United States Public Health Service.

NORTH CAROLINA

New Hospital Near Leaksville.—The Morehead Memorial Hospital, Inc., formally dedicated and opened for patients May 1, is named for the New York philanthropist, John Motley Morehead, a native of Rockingham County, who contributed $100,000 to the building fund. The hospital is located on a 21-acre tract one mile east of Leaksville. It has 112 beds and 19 bassinets. There are no wards in the hospital; rooms are either private or semiprivate and are equipped with hi-low beds and systems for intercommunication with the nurses' stations. The entire building is completely air-conditioned. An intensive care unit of four beds is also available. There are three operating rooms, two delivery rooms, labor rooms, and a four-bed recovery room. Each floor has an examination room. The x-ray department equipment includes deep therapy and portable x-ray machines. The total cost of this hospital project was about $1,700,000. The hospital is owned and operated by a 15-member board of trustees as a nonprofit institution. Mr. William O. Moser is administrator.



The Morehead Memorial Hospital, near Leaksville, N. C.

Propose Institute on Continued Patient Care.—A study aimed at the establishment of an Institute on Continued Patient Care has been launched at the Duke University Medical Center, Durham. Currently being evaluated by state public health officials, welfare leaders, and others, the proposed institute would provide an educational program for workers in various health fields. Purpose of the program would be to mobilize and coordinate health services that are available to patients after their discharge from hospitals. Among persons attending the Duke meeting, held to study the problem of follow-up care and to obtain all possible information for evaluation, were Dr. Roy R. Norton, head of the North Carolina Department of Public Health; Ellen Winston, Ph.D., Raleigh, head of the North Carolina Department of Public Welfare; and Dr. Amos N. Johnson, of Garland, president of the North Carolina Medical Society.

Retired Dean to Head Honor Society.—The retiring dean of the Duke University School of Medicine, Durham, Dr. Wilburt C. Davison, has been elected president of Alpha Omega Alpha, national Honor Medical Society. Dr. Davison retired as dean of the Duke Medical School on July 1, and will retire from the faculty in August, 1961. During his final year, he will continue as James B. Duke Professor of Pediatrics. The first and only dean of the Duke Medical School, Dr. Davison came to Duke in 1927 from the assistant deanship at Johns Hopkins School of Medicine. A member of the honor society's board of directors, he succeeds Dr. Walter Lawrence Bierring, of Des Moines, Iowa, who has been president since 1924. Alpha Omega Alpha is a nonsecret college medical honor society dedicated to the attainment of the "highest ethical and professional standards," and membership is based on scholarship, personal honesty, and potential leadership.

PENNSYLVANIA

Dr. Dailey Named Hospital Administrator.—Dr. W. Paul Dailey was appointed medical administrator at the Harrisburg Hospital, effective June 1. He has been a member of the medical staff of the Harrisburg Hospital since 1933, limiting his practice to obstetrics, and has been director of the department of obstetrics and gynecology since 1947, and chief of staff since 1957. Dr. Dailey is also clinical professor in obstetrics on the faculty of Hahnemann Medical College, a position he had held since 1950. He succeeds Dr. John G. Knauer who has filled the administrative position since 1953.

Society News.—At the annual business meeting of the Pennsylvania Academy of Physical Medicine and Rehabilitation the following officers for the year 1960-1961 were elected: president, Dr. Nathan Sussman, Harrisburg; vice-president, Dr. Robert G. Stevens, Williamsport; and secretary-treasurer, Dr. J. Murl Johnston, Pittsburgh.——At the annual meeting of the Pennsylvania Radiological Society May 13, the new officers were elected for 1960-1961 as follows: Drs. Carl B. Lechner, Erie, president; Robert P. Barden, Philadelphia, president-elect; Peter E. Ringawa, Naticoke, first vice-president; Lester M. J. Freedman, Pittsburgh, second vice-president; Frederick R. Gilmore, Clearfield, secretary-treasurer; John H. Harris Jr., Philadelphia, editor; Marlyn W. Miller, Altoona, associate editor; John H. Harris, Harrisburg, councilor to American College of Radiology; and Newton Hornick, Pittsburgh, alternate councilor..

Philadelphia

Jefferson to Accept Women Students.—Women students are eligible for admission to the Jefferson Medical College, William W. Bodine, president of the institution announced June 7 following action by the board of trustees. The board endorsed a unanimous recommendation of the executive faculty. As a result, 84 of the nation's 85 medical colleges are now coeducational. The Women's Medical College of Pennsylvania accepts only women. Jefferson, reportedly the largest private medical college in the nation, admits a freshman class of 175.

Appoint Co-Chairman for Surgery Department.—Dr. George P. Rosemond has been promoted to professor and co-chairman of the department of surgery, Temple University School of Medicine, it was announced by Dean Robert M. Bucher. Dr. Bucher said that "the unprecedented appointment was made in recognition of the tremendous increase in the surgical service and teaching responsibilities at Temple." Dr. Rosemond will share department obligations with Dr. W. Emory Burnett, head of the department since 1944. Dr. Rosemond, who graduated from the Temple University School of Medicine in 1932, is a diplomate of the American Board of Surgery. He holds other surgical appointments at the Philadelphia General Hospital, St. Christopher's Hospital for Children, and the Episcopal Hospital.

Personal.—Dr. John Franklin Huber, head, department of anatomy, Temple University Medical Center, was named chairman-elect of the Council on Medical Television of the Institute for Advancement of Medical Communication. This group is a national organization comprised of physicians and scientists who have had experience or are interested in the various uses of television in medical communication and education as well as a tool in research and diagnosis.——Dr. Isidor S. Ravdin, vice-president for medical affairs at the University of Pennsylvania, on June 13 was cited by Lehigh University for his "contributions to medicine and higher education." He received the honorary degree of doctor of science during the 92nd commencement exercises.

Laboratory for Cystic Fibrosis Research.—A laboratory to carry out research in cystic fibrosis at the Temple University School of Medicine was jointly announced by the dean, Dr. Robert M. Bucher, and Dr. Wynne Sharples, president of the newly formed Cystic Fibrosis Research Institute of Pennsylvania, Inc. Dr. Sharples stated that the research effort at Temple University will constitute the major activity supported by the new institute. Institute headquarters are located at the Fidelity Philadelphia Trust Building where the other phase of its work, dissemination of information to the medical profession is carried out. A research director, who will also be appointed to the staff at Temple University, will supervise the new laboratory, where a program of basic approach to the disease will be initiated. Dr. Sharples is the founder and former president of the National Cystic Fibrosis Research Foundation, from which she resigned last January after a five-year association. In addition to Dr. Sharples, officers of the institute are Dr. Ruth H. Weaver, director of the division of medical services of the Philadelphia Board of Education, vice-president, and Mr. Frank C. P. McGlinn, vice-president of the Fidelity Philadelphia Trust Company, treasurer.

TEXAS

County Society Offers Scholarship.—The Nueces County Medical Society, Corpus Christi, is offering a $1,000 a year scholarship to a qualified student from its area. The grant, which would continue for four years of medical training, is reportedly the second to be offered by a county medical society. Dr. James R. Riley, president of the society, said that the purpose of the program was to "promote interest in medicine as a profession among talented people who might be prevented from entering by the high cost of a medical education."

Dr. Knight Named Assistant Dean.—Appointment of Dr. James A. Knight as assistant dean of Baylor University College of Medicine in the Texas Medical Center, Houston, was announced June 22. The appointment is effective July 1. Dr. Knight will take over certain of the student personnel activities and will retain teaching and clinical responsibilities in the department of psychiatry to which he was appointed in 1958 and where he holds the rank of assistant professor. Dr. Knight, a native of St. George, S. C., served on active duty with the U. S. Navy as a chaplain during World War II, and later entered Vanderbilt University School of Medicine, where he received his M.D. degree in 1952.

WEST VIRGINIA

State Association Selects Scholarship Winner.—Mr. Harry Glenn Buchanan, of Gilbert, Mingo County, was selected by the Medical Scholarships Committee, West Virginia State Medical Association, as the 1960 recipient of the four-year scholarship award to the West Virginia University School of Medicine. Announcement of the award was made by Dr. Carl B. Hall, of Charleston, chairman of the committee. The scholarship, worth $4,000, is awarded annually to a student enrolled in the first-year class at the

School of Medicine. The award will be presented formally during the 93rd annual meeting of the State Medical Association at The Greenbrier, White Sulphur Springs, Aug. 25-27. Mr. Buchanan will begin his studies in September as a freshman in the WVU School of Medicine. The State Medical Association's scholarship program became effective in 1958.

Personal.–Dr. Emma Jane Freeman, of Buckhannon, was appointed director of the Division of Maternal and Child Health of the West Virginia State Department of Health. Dr. Freeman, who succeeds Dr. Theophilus H. Boysen, III, who resigned late in May to engage in private practice outside of West Virginia, assumed her new duties in Charleston on July 1.——Dr. Charles A. Zeller, chief of psychiatry, Southwestern State Hospital, Marion, Va., since July 1, 1958, was named superintendent of Weston State Hospital to succeed Dr. Robert P. Hagerman, who resigned to accept appointment as director of the Department of Mental Health. Dr. Zeller served as superintendent of Weston State Hospital from 1949 until 1951, when he resigned to accept appointment as chief psychiatrist at the VA Hospital in Clarksburg, a post he held until accepting appointment at the Virginia institution in 1958.

GENERAL

Conference on Ultrasonics.–The American Institute of Ultrasonics in Medicine will hold its second international conference on Aug. 20 at the Statler-Hilton Hotel in Washington, D. C. The chairman of the program committee is Dr. Dorothy M. Stillwell, department of physical medicine and rehabilitation, University of Colorado Medical Center, Denver 20. Those persons interested in presenting a paper at the scientific portion of the meeting should send an abstract of not more than 250 words to the program chairman for consideration.

Changes on National Advisory Committee.–Dr. Franklin D. Yoder resigned as a member of the National Advisory Committee on which he represented the public health area. His reason for doing so is that because of his appointment as Director of the Division of Environmental Medicine, American Medical Association, he will not be an active practitioner in the field of public health. Dr. Yoder was formerly director of the Wyoming State Department of Public Health. The President appointed, as Dr. Yoder's successor, Dr. Richard K. C. Lee, Honolulu, president of the State Board of Health of Hawaii, as representative of the health area on the National Advisory Committee.

International Gerontology Meeting in San Francisco.–The fifth congress of the International Association of Gerontology will be held in San Francisco Aug. 7-12, and all sessions will be held in the Civic Center Auditorium. On Aug. 7 and Aug. 8, general symposiums are scheduled on "Appraisal of Approaches to Aging" and "Meaningful Use of Free Time." The program is arranged in four sessions which will hold concurrent meetings each day under the following general headings: biological sciences, clinical medicine, psychology and the social sciences, and social welfare. General symposiums are also planned for Aug. 10 by the section on biological sciences and Aug. 12 by the section on clinical medicine. For information, write the president of the congress, Mr. Louis Kuplan, P. O. Box 2103, Sacramento 10, Calif.

Society News.–At the annual meeting of the Society for Investigative Dermatology the following officers were elected: president, 1960-1961, Dr. Harvey Blank, Miami; vice-president, 1960-1961, Dr. Stephan Epstein, Marshfield, Wis.; secretary-treasurer, 1960-1965, for third term, Dr. Herman Beerman, Philadelphia; board of directors, 1960-1965, Dr. John M. Knox, Houston, Texas, and Dr. Richard B. Stoughton, Cleveland.——The following officers were elected at the 20th annual meeting of the American Diabetes Association June 12: Drs. Franklin B. Peck Sr., president, Indianapolis; Blair Holcomb, first vice-president, Portland, Ore.; Jerome W. Conn, second vice-president, Ann Arbor, Mich.; E. Paul Sheridan, secretary, Denver; and Thomas P. Sharkey, treasurer, Dayton, Ohio. Dr. Charles H. Best, of Toronto, Canada, was elected an honorary president. Dr. Elliott P. Joslin, of Boston, also is an honorary president of the association.

Increase in Medical News Media.–The *Wall Street Journal* reported June 23 that more media are competing for the 75 minutes a day which a survey finds doctors spend on keeping up with medical news. Recent entries include *Medical World News*, "Medicolegal Digest," and "Journal of New Drugs and Factor," which specializes in psychiatry. A new weekly tabloid, *Medical Tribune*, plans to become a daily next year. Most of the new publications go free to physicians, with drug advertising paying the costs. "Voice of Medicine," a bi-monthly "journal on records," is also available. Doctors will get their own closed-circuit radio network in January, when R. C. A. plans to start beaming music, medical news, and drug advertisements into doctors' offices in several cities. Starting in September, a New York service called Mediphone plans to help doctors with prescription drug problems by answering their collect calls from anywhere in the U. S. Drug makers will man the phones 24 hours a day.

Increase in Marriages.–Last year about 1,505,000 couples were married, it is reported by statisticians of the Metropolitan Life Insurance Company. This was an increase of 2.7% over the number of marriages in 1958, and reversed a two-year downward trend. The 1,465,000 marriages in 1958 was the smallest number in any year since the close of World War II. Most states reported more marriages in 1959 than the year before. Alabama and Arkansas led the list with increases of 25% and 19%, respectively, while Florida had an increase of nearly 12%. Mississippi, where the age for marriage was raised in July, 1958, saw the number of marriages drop to 20,400 last year, as contrasted with 36,400 in 1958 and 62,500 in 1957. Other states showing drops in marriages were Oklahoma, Vermont, New York, Minnesota, Maryland, West Virginia, and Idaho. Memphis and Mobile, near the Mississippi border, led the cities of 100,000 population and over in increased marriages, with gains of 61% and 40%, respectively.

Biological Photography Meeting.—The 30th annual meeting of the Biological Photographic Association will be held Aug. 23-26 in Salt Lake City, Utah, with the Intermountain Chapter acting as host. Field photography, motion pictures, and photomicrography are among the topics to be considered at the meeting, the second national meeting to be held in the West. Besides displays of award-winning photos and slides from clinical photography, there will be professional, institutional, and sequence films shown. A workshop will be held on photography used in educational television and on audiovisual aids. Social activities are planned for wives and families. The Biological Photographic Association is a professional society "dedicated to the advancement of the skills of medical and biological photography," and its world-wide membership includes physicians, medical editors, educators, and institutional staff photographers. Correspondence should be addressed to Mr. Carroll H. Weiss, Director of Communications, 160 Riverside Drive, New York 24, N. Y.

Invite Applications for Nutrition Research Funds.—Applications for financial grants to the Wesson Fund for Medical Research and Education are being accepted. Requests from nonprofit research centers at universities, hospitals, and laboratories, as well as applications from private individuals whose primary work is in nutritional research, will be screened by a medical advisory board which held its organizational meeting in Miami Beach in June. Applicants should direct their written requests to the Wesson Fund, No. 1 E. 45th St., New York 17. The newly established annual grant of $100,000 for basic and clinical research in edible fats and oils will be used to help "those researchers who heretofore have been restricted by a lack of funds." All decisions on granting the awards would rest with the medical advisory board. Members of the board are Dr. Grace A. Goldsmith, New Orleans, representing biochemistry and nutrition; Dr. Robert L. Jackson, Columbia, Mo.; Dr. Joseph Kirsner, Chicago, representing gastroenterology; Dr. Herbert Pollack, New York City, representing internal medicine and nutrition; and Dr. Howard B. Sprague, of Boston.

Joint Meeting with Chest Physicians Planned.—By action of the Board of Trustees of the American Medical Association and the Board of Regents of the American College of Chest Physicians, a joint scientific program will be developed by the Committee on Scientific Program of the American College of Chest Physicians and the Section on Diseases of the Chest of the American Medical Association. This program, to be presented at the 1961 annual meeting of the American Medical Association in New York City, will be the first joint meeting in the history of the two societies. The college will shorten its annual meeting by one day, with its scientific sessions opening on the Saturday preceding the meeting of the A. M. A., instead of Friday as has been the custom during the past quarter of a century. The joint sessions with the Section on Diseases of the Chest of the American Medical Association will be held on Monday and Tuesday following the college meeting. Fireside conferences will be held on Monday night during the A. M. A. meeting instead of Friday night as at past meetings. This will also be a joint session sponsored by both the A. M. A. and the college. Round-table luncheon meetings will be extended to Monday.

Report on Poisoning.—Very young children account for about one-fourth of the 1,400 deaths each year from poisoning by solids and liquids, it is reported by statisticians of the Metropolitan Life Insurance Company. The relative frequency of such poisonings has been declining in recent years—from 11.0 per 1,000,000 population at all ages in 1949 to 8.2 in 1957—the statisticians point out. The death rate is particularly high between ages 1 and 2, drops to a minimum during the school ages, and rises to a secondary peak at ages 45-64. Barbituric acid and its derivatives are the major cause of fatal poisoning among adults in the 25-64 age range, with wood and denatured alcohols ranking second. More than 80% of the alcohol poisoning deaths are among males, while the barbiturates take a somewhat greater toll among women. California residents account for about one-third of the reported deaths from barbiturates in the United States. Under age 5, drugs and medicines (other than barbiturates) are the most frequent killers. More than half the deaths from aspirin and other salicylates are among children in this age group. Among the other causes of fatal poisoning in the preschool group are kerosene and other petroleum products, lead and its compounds, and household pesticides containing arsenic compounds or other lethal ingredients.

Indian Physician Awarded Rehabilitation Fellowship.—The World Rehabilitation Fund, Inc., announced the awarding of a Charles Poore Jr., Memorial Fellowship to Dr. Mary Verghese, India. The fellowship was created by the World Rehabilitation Fund with a contribution from the IBM World Trade Corporation to honor the late Charles Poore, an employee of the trade corporation who became a quadriplegic while serving in Saudi Arabia. Mr. Poore underwent treatment and rehabilitation at the Institute of Physical Medicine and Rehabilitation, New York University Medical Center and returned to work with IBM World Trade Corporation in New York City. He died of complications of his disability. Dr. Mary Verghese is a member of the staff of the Christian Medical College Hospital, Vellore, India, and is currently enrolled in postgraduate training in the department of physical medicine and rehabilitation, New York University Medical College. Dr. Verghese is confined to a wheelchair resulting from an automobile accident in 1954. The Charles Poore Memorial Fellowships is also to be supported through a contribution of Mrs. David M. Heyman, New York City, to the Institute of Physical Medicine and Rehabilitation specifically for this purpose. The World Rehabilitation Fund is a nonprofit organization supported by American industry, foundations, and individuals to assist in the international development of rehabilitation services for the physically handicapped.

Exhibit of Early Surgical Books in Chicago.—An exhibit of early books on surgery may be seen at the American College of Surgeons, 40 E. Erie St., Chicago. Books on display are from the H. Winnett Orr Historical Collection and other donations to the college library, numbering more than 2,300 items and including early illustrated anatomical treatises. Also on display is a collection of early American surgical instruments, presented to the college by Smith Kline & French Laboratories of Philadelphia. Two of the oldest books in the display are by Avicenna, 980-1037 A. D. His *Flores* was printed in Lyon in 1508, and the two-volume *Canon,* in Latin, printed in Venice in 1520, became the text and law for the practice of medicine throughout Europe for 600 years. Second oldest book in the exhibit is the *Rosa Gallica* by Symphorien Champier, a first edition, printed in Paris in 1514. Champier, 1472-1539, was one of the first to write medical history and bibliography. This is a work on medicine, botany, and cookery, with sections on sleep, exercise, and accidents of the mind. The author quotes from Hippocrates, Galen, and Avicenna. Dr. H. Winnett Orr, of Lincoln, Neb. (1877-1956), spent more than 25 years locating important early books dealing with surgery. A "Catalogue of the H. Winnett Orr Historical Collection" and other rare books in the library of the American College of Surgeons is available. For information, write The American College of Surgeons, 40 E. Erie St., Chicago 11.

Clinical Congress for Surgeons.—The 46th annual clinical congress of the American College of Surgeons will be held in San Francisco, Oct. 10-14. Dr. Leon Goldman, chairman, department of surgery, University of California School of Medicine, Berkeley–San Francisco, is chairman of the local committee on arrangements. Major addresses will be made by Dr. Isidore S. Ravdin, Philadelphia, chairman, board of regents, and incoming president of the college; Dr. Joseph Trueta, Oxford, England, who will speak on trauma and the living cell; Wendell M. Stanley, Ph.D., director of the virus laboratory, University of California, Berkeley, and Nobel winner in chemistry, who will deliver the Martin Memorial Lecture, on virus-cancer relationships; and Mr. Leslie Philip Le Quesne, London, who will give the annual Baxter Lecture, speaking on body fluid disturbances resulting from stomach obstruction. Nine postgraduate courses will be offered. The surgical forum sessions will present 258 reports, and operations will be telecast from Stanford University Medical Center. Motion pictures are scheduled, and panel sessions in general surgery, and in the surgical specialties of gynecology and obstetrics, neurologic surgery, orthopedic surgery, plastic surgery, thoracic surgery, and urology will be held throughout the five-day meeting. Headquarters will be the Civic Auditorium. Dr. Owen H. Wangensteen, Minneapolis, is retiring president of the college. Dr. Paul R. Hawley, 40 E. Erie St., Chicago, is the director.

International Congress on Occupational Health.—The 13th International Congress on Occupational Health will be held at the Waldorf–Astoria Hotel, New York City, July 25-29, the first such congress to be held in the U. S., and more than 2,500 industrial physicians, nurses, and hygienists from more than 43 different countries are expected to attend. Members of the A. M. A. Council on Occupational Health, including Dr. William P. Shepard, of New York City, Dr. Melvin N. Newquist, West Cornwall, Conn., and Dr. Robert A. Kehoe, of Cincinnati, have been active in preparing for this meeting. Dr. E. Vincent Askey, President of the A. M. A., will give one of the welcoming addresses. The program will include sessions on *Administrative Practices;* Toxicology; Heat Stress and Strain; Mental Health; Exposure to Ionizing Radiation; *Pneumoconioses;* Health and Accident Statistics; International Cooperation in Occupational Health; Lead Poisoning; *Respiratory Disease;* Fundamental Physiological Responses; Social and Legal Aspects; Noise, Vibration and Illumination; Poisoning; *Work Physiology and Psychology;* Analytical Procedures; Labeling; Social Medicine; Dermatitis; Rehabilitation; *Education and Training;* Maximum Allowable Concentrations; Caisson Disease; Control of Ionizing Radiation; *Radiation Effects;* and Applied Psycho-Physiology (sessions in italics refer to major sessions at which simultaneous translation will be available). Arrangements have been made for 23 field trips to toxicology research laboratories, industrial plants, governmental health and industrial hygiene institutions, and educational centers for industrial health. Programs and registration and reservation forms may be obtained from Dr. Robert E. Eckardt, Secretary-General, 13th International Congress on Occupational Health, 527 Madison Ave., New York 22.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	June 16, 1960		June 20, 1959
	Paralytic Type	Total Cases	Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	..	..	..
Rhode Island	5	5	..
Connecticut	..	..	..
Middle Atlantic States			
New York	..	..	3
New Jersey	..	..	..
Pennsylvania	..	1	..
East North Central States			
Ohio	..	..	3
Indiana	..	..	1
Illinois	3	3	2
Michigan	1	1	2
Wisconsin	..	..	1
West North Central States			
Minnesota	2	2	..
Iowa	..	..	17
Missouri	..	..	1
North Daokta	..	..	..
South Dakota	..	..	..
Nebraska	..	..	..
Kansas	..	1	2
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	..
West Virginia	..	..	1
North Carolina	..	..	4
South Carolina	2	3	..
Georgia	..	..	2
Florida	1	1	2
East South Central States			
Kentucky	..	1	2
Tennessee	..	..	1
Alabama	..	..	2
Mississippi	..	..	1
West South Central States			
Arkansas	..	..	7
Louisiana	..	..	4
Oklahoma	..	..	2
Texas	1	1	15
Mountain States			
Montana	..	..	..
Idaho	..	..	1
Wyoming	..	..	..
Colorado	..	..	..
New Mexico	..	1	..
Arizona	..	..	1
Utah	..	..	..
Nevada	..	..	..
Pacific States			
Washington	..	..	3
Oregon	3	4	1
California	12	13	3
Alaska	..	..	..
Hawaii	..	..	..
Territories and Possessions			
Puerto Rico	35	36	..
Total	65	73	84

Family Institute to Treat Mental Illness.—Formation of the Family Institute, a new national organization to combat and treat mental illness on a family, rather than an individual basis, was announced June 14 by Mrs. Anne W. Langman, president. Chairman of the new organization is Dr. Nathan W. Ackerman, associate clinical professor of psychiatry at Columbia University College of Physicians and Surgeons, New York City. The over-all objective of the new institute, which will have offices at 10 E. 44th St., New York 17, is "to evolve a comprehensive program for the enhancement of the mental health of families through research, diagnostic and educational activities." It will offer program assistance to more than 600 family agencies and counseling centers throughout the country. Mrs. Richard W. Dammann will serve as executive director of the new organization. The institute plans to:

- Establish a training program in the techniques of family psychotherapy for psychiatrists, psychologists, social workers, and members of other professions concerned with mental health.
- Initiate Family Mental Health Clinics in such places as *hospitals, psychiatric and psychoanalytic institutes, and family agencies.*
- Produce and distribute training, teaching, and research films to universities, medical schools, psychiatric associations, family agencies, and other professional societies and organizations.
- Sponsor an annual meeting for representatives of the various professions concerned with family problems.
- Publish a professional journal which reflects advances in the field of family mental health.
- Promote and execute research on problems of family development and relationships.

Directors of the institute include Dr. Martin Cherkasky, New York City; Dr. Iago Galdston, New York City; Dr. Roy R. Grinker, Chicago; and Dr. Donald D. Jackson, Palo Alto, Calif.

CANADA

Anesthesiologists to Hold Congress.—The second World Congress of Anaesthesiologists will be held in Toronto, Ontario, Canada, Sept. 4-10, under the auspices of the Canadian Anaesthetists' Society. The congress is open to all interested physicians, and contributions of papers on clinical anesthesia, clinical and laboratory investigation, physiology, pharmacology, biochemistry, biophysics in relation to anesthesia, and organization and teaching are invited from members of the World Federation of Societies of Anaesthesiologists and from associate members throughout the world. The papers to be given in the plenary sessions, Sept. 5-9, must not exceed 20 minutes duration. Papers for the concurrent sessions will be of 10 minutes duration. French, German, Spanish, and English will be the official languages, and the congress will include a commercial exhibition of apparatus, instruments, and drugs employed in anesthesiology. All correspondence should be directed to The Second World

Congress of Anaesthesiologists, 178 Saint George St., Toronto 5, Ontario, Canada.

FOREIGN

Rheumatology Meeting in Rome.—The 10th International Congress on Rheumatoid Diseases will take place in Rome, Italy, Sept. 4-7, 1961, at the E. U. R. Building. Official languages of the congress will be English, French, Spanish, German, and Italian, and simultaneous translation will be provided. Subjects to be considered will be confined to rheumatology from a clinical and biological standpoint. Four days of lectures, reports, and symposiums are scheduled. Persons who wish to contribute to the scientific section of the program are asked to submit a title and 200 word summary in triplicate to the scientific committee before Dec. 31. An English and French translation are requested. All correspondence should be addressed to the General Secretary of the Congress, Prof. C. B. Ballabio, Clinica Medica, Generale Via F. Sforza 35, Milano, Italy. Postcongress tours to Naples, Florence, Tarquinia, and Venice will be arranged.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Dermatology: Final date for filing applications of candidates completing training by October 15, 1960 is March 1, 1961. *Written.* Several cities, June 5, 1961. *Oral.* Philadelphia, Oct. 13-16, 1961. Sec., Dr. Maurice J. Costello, One Haven Avenue, New York 32, New York.

American Board of Internal Medicine: New York City, Nov. 14-17. Closing date for filing application was July 1. *Written.* Oct. 17. Closing date for filing application was May 1. Schedule for 1961. *Written Examination,* October 16. *Oral Examinations.* New Orleans, Jan. 30-Feb. 2; Chicago, April 4-7; Los Angeles, Sept. 26-29; New York City, Nov. 7-10. Closing date for acceptance of applications for the January and April examinations is October 1, 1960, and for the September and November examinations is June 1, 1961. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. *Oral.* New Haven, Nov. 6-9. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: *Written.* Various cities of the United States, Canada, and military centers outside of continental United States, January 13. Application for certification, new and reopened in Part I, and requests for reexamination in Part II are now being accepted. Deadline for receipt of applications is August 1. Candidates submitting applications in 1960 for the 1961 examinations are not required to submit case reports as previously required to complete the Part I examination. In lieu of this requirement, new candidates are required to keep in their files a duplicate list of hospital admissions as submitted with their application, for submittal at the annual meeting in Chicago should they become eligible to take the Part II (oral) examination. Reopened candidates will be required to submit case reports for review thirty days after notification of eligibility. Exec. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications was July 1. *Oral* Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

American Board of Orthopaedic Surgery: *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing applications was July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral.* Chicago, Oct. 3-6. Final date for filing application was April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pathology: *Examination.* Indianapolis, Oct. 20-22. Final date for filing application is Sept. 15. Sec., Dr. Edward B. Smith, 1100 W. Michigan St., Indianapolis 7.

American Board of Pathology: *Examination. Special Field of Forensic Pathology.* New Orleans, Nov. 13. Final date for filing application is Oct. 1. Sec., Dr. Edward B. Smith, 1100 W. Michigan St., Indianapolis 7.

American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Plastic Surgery: Entire examination—*written,* and *oral* and *practical* given in May of each year. Final date for submitting case reports is November 1. Next examination to be given in New York City, May 1961. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Parts I and III.* Philadelphia, Sept. 24. Final date for filing application was June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: New York, New York, Dec. 12-13, New Orleans, Mar. 20-21, 1961. Sec., David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnati, Dec. 10-13. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination was July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Written.* (Part 1), Various Centers, Dec. 7. *Candidates are urged to apply several months before completion of training requirements.* The closing date for filing applications is August 1. Those completing training requirements after September 30 cannot be considered for the December Part I examination of the same year. *Oral.* (Part II)—New Haven, Sept. 26-27; Indianapolis, Oct. 24-25; Buffalo, Nov. 14-16; Nashville, Dec. 12-13; Philadelphia, Jan. 16-17; Houston, Feb. 13-14; Columbus, Ohio, Mar. 13-14; New York City, April 19-20; Portland, Ore., May 15-16; San Francisco, May 18-19. No examinations will be held in June, July or August. Sec.-Treas., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

Board of Thoracic Surgery: *Written.* Various centers throughout the country, Sept. 9. Final date for filing application was July 1. *Oral.* Oct. 1960. Final date for filing application is July 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

DEATHS

Baron, William Ⓜ St. Louis; Marion-Sims College of Medicine, St. Louis, 1899; associated with the Alexian Brothers Hospital, where he died May 11, aged 88, of cerebral hemorrhage.

Blue, John Howard, Montgomery, Ala.; Columbia University College of Physicians and Surgeons, New York City, 1901; fellow of the American College of Surgeons; veteran of World War I; for many years associated with St. Margaret's Hospital; served as surgeon to the Louisville and Nashville Railroad, Western Railroad of Alabama, Seaboard Air Line Railroad and Alabama Power Company; a director of the Alabama National Bank and Durr Drug Company; died May 6, aged 82, of cerebral vascular accident.

Campbell, Mary Mumford, Meadville, Pa.; Cleveland Homeopathic Medical College, 1901; for many years a member of the board of health of Meadville; first president of the Crawford County Cancer Society; served as school physician; formerly member of the board of directors of the Meadville City Hospital, where she died May 7, aged 82, of a fractured hip as the result of a fall.

Chaffee, Festus Mahlon Ⓜ Middlesex, N. Y.; Syracuse University College of Medicine, 1902; veteran of World War I; served as Middlesex health officer and county coroner for many years; formerly associated with the medical staff at Eastman Kodak Company in Rochester, N. Y.; associated with the Frederick Ferris Thompson Hospital in Canandaigua and Soldiers and Sailors Memorial Hospital in Penn Yan, where he died May 8, aged 81, of cerebral embolism.

Davidson, Sol Charles, Rochester, N. Y.; Albany (N. Y.) Medical College, 1912; specialist certified by the American Board of Radiology; member of the American Roentgen Ray Society, Radiological Society of North America, and the American College of Radiology; served in France during World War I; clinical instructor in the department of radiology at the University of Rochester School of Medicine and Dentistry; associated with the Strong Memorial Hospital and the Highland Hospital, where he died May 9, aged 72, of epithelioma of the face and neck.

Engelsher, David Louis Ⓜ New York City; University and Bellevue Hospital Medical College, New York City, 1919; associate clinical professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals; fellow of the American College of Allergists; associated with the Fordham Hospital, Morrisania Hospital, and the Bronx Eye and Ear Infirmary; died May 10, aged 69, of acute coronary occlusion.

Fulton, John Farquhar Ⓜ Sterling professor of the history of medicine at Yale University School of Medicine in New Haven, Conn., died at his home in Hamden, Conn., May 29, aged 60, of arteriosclerotic heart disease with recurring congestive failure, diabetes mellitus, and cerebral accident. Dr. Fulton was born in St. Paul, Minn., on Nov. 1, 1899. He was a student at the University of Minnesota from 1917 to 1918, and in World War I was stationed at Fortress Monroe. In 1921 he received his bachelor of science degree from Harvard, where in 1927 he received his medical degree. He was named a Rhodes Scholar at Oxford from 1921 to 1923 and a Christopher Welch Scholar for the next two years. From Oxford he received the bachelor of arts degree in 1923, the master of arts and doctor of philosophy degree in 1925, and the doctor of science degree in 1932. From 1923 to 1925 he served as a demonstrator in physiology at Oxford, was a research assistant in physiology at Harvard from 1925 to 1928, was associate in neurological surgery at Peter Bent Brigham Hospital in Boston in 1928, and in 1928 to 1930 was a demonstrator in physiology and a fellow of Magdalen College, Oxford. He joined the faculty of Yale University School of Medicine in 1929 as professor of physiology and was named a Sterling professor in 1930. In 1951, when he relinquished his physiology professorship for the history of medicine post, he was also chairman of the department of physiology. Next fall he was to have been chairman of the Yale department of the history of science and medicine, announced this winter as a new university-wide program to include undergraduate, graduate, and medical students. In 1956 he was honored by more than 100 of his former students and colleagues on his 25 years of service to Yale. He received a silver medal and a bound copy of a special issue of the *Yale Journal of Biology and Medicine* dedicated to him. The issue contained articles by more than 30 contributors, all of whom were former students or associates. His pioneer work in neurophysiology during the 1920's and 1930 outlined the basic concepts of the workings of the brain and later led to the development of the operation known as frontal lobotomy. He and an associate reported on their brain research at an international neurosurgical conference in 1935. The report lead Egas Moniz of Portugal, who was in the audience, to extend the animal research to human patients, and Moniz in 1949 received the Nobel Prize for his work. During World War II Dr. Fulton headed the Yale Aero-

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Ⓜ Indicates Member of the American Medical Association.

medical Research Unit that developed a high altitude flying suit for pilots and worked on leading physiological problems connected with aviation medicine. For his contribution to the allied war effort in the scientific field he was made a honorary officer of the Civil Division of the Order of the British Empire. He was also an Officer of the French Legion of Honor, a Commander of the Order of Leopold of Belgium, and had received the Order of Cultural Merit, Class II, of Rumania, the gold medal of the University of Liege, Belgium, and the Order of Merit, Carlos J. Finlay, of Cuba. In 1939-1940 he was vice-chairman of the Section on Nervous and Mental Diseases of the American Medical Association, and served as vice-president of the Medical Library Association. He was a member of the Harvey Cushing Society, Association for Research in Nervous and Mental Disease, of which he was past-president, and the Aero Medical Association. He was past-president of the Association of Honorary Consultants of the Army Medical Library and the History of Science Society, which in 1958 presented him with its first annual George Sarton Medal, given annually for "outstanding contributions in history of science." In 1955 the society honored him by establishing the John F. Fulton Medal and made him the first recipient. He was a member of the board of trustees of the Institute for Advanced Study at Princeton University since 1942. Since the establishment at Yale in 1940 of the Historical Library he was chairman of its advisory board. He was also keeper of medical history collections and chairman of the Yale Medical Library Committee. He occupied a number of distinguished lectureships, and many honors came to him in this country and abroad. In 1957 he received an honorary doctor of letters degree from Oxford, giving him a total of five degrees, four of them earned from Oxford. He also received honorary degrees from Yale, Kenyon, Emory, and Boston University, in this country, and from abroad he also received honorary degrees from the universities of Birmingham, Oslo, and Louvain. He was the author of many leading publications. Medical texts include "Muscular Contraction" (1926), "Physiology of the Nervous System" (1936–revised in 1943, 1949, with translations in French, German, Portuguese, and Russian), and revisions of Howell's well known "Textbook of Physiology." In 1946 Dr. Fulton published his biography of Dr. Harvey Cushing. Dr. Fulton was a close colleague of Dr. Cushing and was responsible for persuading Dr. Cushing to spend the last years of his life at Yale. In 1947 in collaboration with Miss Elizabeth H. Thomson, Dr. Fulton published the "Life of Benjamin Silliman" in conjunction with the centennial of the Sheffield Scientific School at Yale. He was also the author of studies of Robert Boyle, Giralomo Fracastoro, Joseph Priestley, Richard Lower, John Mayow, and Sir Kenelm Digby. He was associate editor of "War Medicine" and from 1940 to 1945 was chairman of the editorial board of "Medical History of the War." In 1945 he received a citation from the War Department for his work with the Army Medical Library.

Greenhouse, Jerome Mayer Ⓢ Hollywood, Fla.; St. Louis University School of Medicine, 1939; specialist certified by the American Board of Dermatology; fellow of the American Academy of Dermatology and Syphilology; veteran of World War II; clinical instructor in dermatology at the University of Miami School of Medicine in Coral Gables; chief of the dermatology section, Memorial Hospital; formerly practiced in St. Louis; died April 4, aged 44, of coronary thrombosis.

Griffith, Joseph Myrhl Ⓢ Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1919; associated with the White Cross Hospital; died May 1, aged 66, of pulmonary embolism.

Haggard, Daniel Carr, Fort Worth, Texas; Chattanooga (Tenn.) Medical College, 1910; veteran of World War I; died April 28, aged 80, of heart failure.

Halliday, David James, Kenmare, N. D.; born in Gainsborough, Sask., Canada, in 1898; University of Manitoba Faculty of Medicine, Winnipeg, Man., Canada, 1924; fellow of the American College of Surgeons; member of the American Academy of General Practice; past-president of the North Dakota State Medical Association and the state board of medical examiners; associated with the Kenmare Deaconess Hospital, where he was president of the hospital board; served as alderman on the city council from 1936 to 1940; past-president of the Kenmare Association of Commerce; a director of the Kenmare State Bank; died April 29, aged 61, of coronary thrombosis.

Hambleton, Holland George Ⓢ Los Angeles; Bowdoin Medical School, Brunswick and Portland, Maine, 1915; associated with the Presbyterian Hospital–Olmsted Memorial; died May 3, aged 68, of coronary disease.

Henry, Hugh George Sr., Germantown, N. Y.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1929; member of the American Academy of General Practice; certified by the National Board of Medical Examiners; served with the Canadian Army Medical Corps during World War I; past-president of the Columbia County Medical Society; member of the Chamber of Commerce; on the staff of the Columbia Memorial Hospital in Hudson, where he died April 24, aged 64, of cerebral hemorrhage.

Hibbard, John Van Ord, Greenwich, Conn.; University of Buffalo (N. Y.) School of Medicine, 1906; at one time on the faculty of Columbia University

College of Physicians and Surgeons, New York City; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons; member of the American Urological Association; veteran of World War I; served on the staff of the United Hospital in Port Chester, N. Y., and St. Luke's Convalescent Hospital; died May 4, aged 75, of coronary thrombosis.

Holcombe, Benjamin Jr. Ⓜ Philadelphia; Howard University College of Medicine, Washington, D. C., 1944; an officer in the medical corps, U. S. Army Reserve, from July, 1951, to July, 1953; associated with the Mercy Douglas Hospital; died May 2, aged 42, of acute coronary disease.

Jacobs, Harry, Brooklyn; Long Island College Hospital, Brooklyn, 1921; member of the Industrial Medical Association; died in the Beth Israel Hospital, New York City, Feb. 9, aged 60, of myocardial infarction.

Jones, Henry Orendorf, Sebring, Fla.; Jefferson Medical College of Philadelphia, 1905; died in the Walker Memorial Sanitarium and Hospital, Avon Park, March 1, aged 75, of dissecting aneurysm of the abdomen and arteriosclerosis.

Jones, John William Ⓜ Phoenix, Ariz.; University of Colorado School of Medicine, Denver, 1953; member of the American Academy of General Practice; associated with the Memorial, St. Joseph's, and St. Luke's hospitals, and the Good Samaritan Hospital, where he served an internship, and where he died May 7, aged 36, of myocardial infarction.

Joplin, William Stevens Ⓜ Petersburg, Tenn.; Memphis (Tenn.) Hospital Medical College, 1900; past-president of the Tennessee State Medical Association; director of the First National Bank; on the staff of the Lincoln County Hospital, where he died April 11, aged 84, of myocardial infarction.

Kech, Augustus Sheridan Ⓜ Altoona, Pa.; born in Snow Shoe May 11, 1882; University of Pennsylvania School of Medicine, Philadelphia, 1911; specialist certified by the American Board of Internal Medicine; past-president of the Medical Society of the State of Pennsylvania and the Blair County Medical Society; fellow of the American College of Cardiology and the American College of Physicians; in 1938 member of the House of Delegates of the American Medical Association; served as physician to the State Tuberculosis Clinic from 1911 to 1926; county medical director of Blair County for state department of health from 1919 to 1930; during World War I was a medical member of Altoona draft board number I and during World War II served as an advisory member of that board; first president of the Blair County Mosquito Extermination Commission; interned at the Altoona General Hospital, where he later joined the staff; director of staff and cardiologist, Tyrone (Pa.) Hospital; cardiologist at the Miners Hospital of Northern Cambria in Spangler, consultant and cardiologist at the Veterans Administration Hospital, and in 1938 became chief of the medical service, in 1940 became director of the staff, and served as cardiologist at the Mercy Hospital, where he died May 1, aged 78, of cerebral hemorrhage.

Kibbe, John Halbert Ⓜ Monroe City, Mo.; Jefferson Medical College of Philadelphia, 1922; associated with St. Elizabeth's Hospital and the Levering Hospital, Hannibal, where he died April 26, aged 64, of cerebral hemorrhage.

Kirk, Grover Cleveland, Chambersburg, Pa.; Johns Hopkins University School of Medicine, Baltimore, 1925; veteran of World Wars I and II; certified by the National Board of Medical Examiners; served on the staffs of numerous Veterans Administration hospitals; died April 29, aged 74, of coronary occlusion.

Lauzer, Edward Simon, Cora, Wyo.; University of Nebraska College of Medicine, Omaha, 1905; served as mayor of Rock Springs; died in the Memorial Hospital of Sweetwater County in Rock Springs May 1, aged 78, of arteriosclerotic heart disease.

Lehmann, Richard Ruben, New York City; Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Baden, Germany, 1902; served a residency at the Municipal Sanatorium in Otisville, N. Y., and the Triboro Hospital in Jamaica, N. Y.; died Feb. 28, aged 83, of acute coronary thrombosis.

Levy, Harold H., New York City; Boston University School of Medicine, 1926; died April 30, aged 63, of myocardial infarction and diabetes mellitus.

Lewin, Philip Ⓜ Chicago; born in Chicago June 18, 1888; Rush Medical College, Chicago, 1911; specialist certified by the American Board of Orthopaedic Surgery; professor emeritus of bone and joint surgery and past-chairman of the department, Northwestern University Medical School, where he was a member of the faculty since 1918; professor of orthopedic surgery at the Cook County Graduate School of Medicine; a founder, librarian, and for many years secretary of the American Academy of Orthopaedic Surgeons, which awarded him its Gold Medal; in 1939 was awarded the certificate of merit by the American Roentgen Ray Society and the Silver Medal by the American Medical Association; past-president of the Chicago Orthopedic Society; member of the American Orthopaedic Association, Clinical Orthopaedic Society, International Society of Orthopedic Surgery and Traumatology, and the American Rheumatism Association; founder fellow of the U. S. Chapter of the International College of Surgeons; fellow of the American College of Surgeons; member of the medical advisory committee of the National Foundation for Infantile Paralysis; member of the professional advisory committee, Division Services for

Crippled Children, and member of the advisory board of the division for handicapped, Illinois State Department of Welfare; member of the advisory committee on infantile paralysis, Illinois Department of Public Health; veteran of World Wars I and II; senior attending orthopedic surgeon and past-chairman, department of bone and joint surgery, Michael Reese Hospital; affiliated with Cook County, Municipal Contagious Disease, St. Luke's, and Louis A. Weiss Memorial hospitals; author of many books; died in the Michael Reese Hospital May 13, aged 71, of myocardial infarction and cerebral thrombosis.

Lieberman, David Paul Ⓜ Elizabeth, N. J.; University and Bellevue Hospital Medical College, New York City, 1928; first president of the Union County Pediatric Society; since 1957 member of the board of education; senior attending pediatrician at Elizabeth General Hospital, where he was secretary of the medical board, and St. Elizabeth Hospital; died May 14, aged 57, of coronary occlusion.

Lynn, Clarence Edward Ⓜ Dubuque, Iowa; Rush Medical College, Chicago, 1914; affiliated with the Xavier Hospital, Finley Hospital, and St. Joseph Mercy Hospital, where he died May 3, aged 74, of progressive cardiovascular accident.

McAndrew, James Alfred Ⓜ Lake Bluff, Ill.; Jefferson Medical College of Philadelphia, 1953; interned at the Delaware Hospital in Wilmington; served a residency at the District of Columbia General Hospital in Washington, D. C., where he served a residency at the George Washington University Hospital; from 1956 to 1958 served in the U. S. Navy; died in the Presbyterian–St. Luke's Hospital, Chicago, May 18, aged 32, of acute granulocytic leukemia.

McCarley, Wardlow Howard, Colbert, Okla.; Medical Department of Tulane University of Louisiana, New Orleans, 1893; for many years president of the First National Bank; died April 30, aged 92, of heart failure.

Mansky, Alexander, New York City; Long Island College Hospital, Brooklyn, 1907; died May 1, aged 77, of arteriosclerotic heart disease.

Marks, Morris Samuel, New York City; L. R. C. P., of London, England & M. R. C. S., of England, 1936; died in the Mount Sinai Hospital April 14, aged 50, of cerebral hemorrhage.

Mason, George Eugene Ⓜ Lakewood, Colo.; St. Louis University School of Medicine, 1931; veteran of World War II; died in the Colorado General Hospital in Denver May 7, aged 55, of myocardial infarction.

Parrish, James W., Holliday, Texas (licensed in Texas under the Act of 1907); served as city and county health officer; died in Wichita Falls April 30, aged 85, of cerebral hemorrhage.

Rucker, Pemberton Thomas, Long Beach, Calif.; University of Denver Medical Department, 1894; served on the staff of St. Luke's Hospital in Denver; died in Los Angeles April 13, aged 89, of arteriosclerosis.

Salley, George Elmore, Richmond, Va.; Medical College of Virginia, Richmond, 1954; interned at the Medical College of Virginia, Hospital Division, where he served a residency; served a residency at the Charity Hospital of Louisiana in New Orleans; from 1955 to 1957 served in the medical corps of the U. S. Army Reserve; died in the Richmond Memorial Hospital, May 6, aged 30, of injuries received in an automobile accident.

Schwartz, Samuel H. Ⓜ Plainfield, N. J.; Boston University School of Medicine, 1927; specialist certified by the American Board of Internal Medicine; fellow of the American College of Cardiology and the American College of Physicians; past-president of the Union County Heart Association; veteran of World War II; chief of the electrocardiology division and a senior attending physician at Muhlenberg Hospital; died in Elizabeth City, N. C.; May 8, aged 57, of myocardial infarction.

Shannon, Charles Daniel Ⓜ Seattle; Georgetown University School of Medicine, Washington, D. C., 1915; served in the regular Navy; veteran of World War I; died in the Providence Hospital May 2, aged 68, of subarachnoid hemorrhage.

Solem, George Oliver Ⓜ Oak Park, Ill.; Rush Medical College, Chicago, 1917; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; veteran of World War I; served on the attending medical staff of the Lutheran Deaconess Hospital in Chicago; died May 5, aged 71, of coronary occlusion.

Stokes, J. G. Phelps, New York City; Columbia University College of Physicians and Surgeons, New York City, 1896; died April 8, aged 88, of coronary thrombosis.

Ulmer, David Rust, Terre Haute, Ind.; Barnes Medical College, St. Louis, 1901; past-president of the Terre Haute Academy of Medicine and the Vigo County Medical Society; during World War II awarded the Congressional Medal for examining over 3,000 selectees; on the staff of the Union Hospital where he died April 30, aged 89, of cerebral thrombosis.

Wahl, Stephen Ⓜ New York City; Universität Leipzig Medizinische Fakultät, Saxony, Germany, 1925; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons and the International College of Surgeons; part owner and staff member of the Doctors Hospital in Freeport, where he was a member of the board; on the staff of the Hospital for Joint Diseases; died April 30, aged 59, of coronary disease.

FOREIGN LETTERS

DENMARK

Chylothorax.—Arne Schmidt (*Acta chir. scandinav.* 118:5-12, 1959) analyzed a series of 92 patients with chylothorax. Of these, 62 were of traumatic origin and the rest occurred spontaneously. In most of the traumatic cases, the condition was referable to surgical intervention, especially among the children. In adults, the most frequent trauma was pulmonary operations, which were all performed for tuberculosis and were attended with difficult dissections. In children, cardiovascular surgery was the predominant cause. Thoracic-duct ligation was performed on 42 patients of whom 39 were cured. The condition recurred in three, but no deaths ensued. Conservative treatment was used in 50 patients of whom 36 were cured. The condition recurred in three, and 11 deaths ensued. A closer analysis of these deaths showed that in only four patients was death directly or indirectly referable to chylothorax. Among 20 children who were given conservative treatment, only one death occurred, and this could not be ascribed with certainty to chylothorax. It might be concluded that operative treatment involves only a minimal risk, and that conservative therapy, especially in children, offers a better prognosis than had previously been assumed.

Spontaneous Pneumothorax.—A series of 44 surgically-treated patients with simple pneumothorax was analyzed by Andersen and Poulsen (*Acta chir. scandinav.* 118:105-112, 1959). In this series 23 were treated by inducing pleurodesis, 14 by drainage alone, and 7 by lung resection and decortication or both. Pleurodesis was found to be a suitable treatment in most patients with simple pneumothorax. Drainage alone was reserved for older patients in a generally poor condition, and operation was indicated only in those with large cysts and pronounced pleural thickening (chronic cases). Patients who were examined with a view to the pulmonary function after treatment by thoracotomy with resection of affected segments of the lung and treatment with silver nitrate, respectively, proved to differ so little in this respect that, as far as pulmonary function was concerned, there was no reason to prefer one treatment to the other.

Venous Damage After Sclerosing Injection.—Various experimental and clinical data suggested that damage to the deep veins might occur in the injection treatment for varicose veins, and that the risk of such venous damage could not be definitely assessed except by the number of clinical cases of embolism and deep thrombosis occurring after the treatment. Changes in the deep veins which occur in relation to retrograde injection of a sclerosing solution consist in a less distinct valvular pattern in tilting phlebography and in an increase in the number of fine muscular collaterals. Both must be interpreted as signs of damage to the deep veins.

In order to illuminate these conditions, 68 patients with primary varicose veins were studied by phlebography before and after sclerosing injection, and 109 patients subjected to operation without sclerosing injection were used as controls by Frits R. Matiesen (*Acta chir. scandinav.* 118:155-166, 1959). In these studies, the previously-mentioned phlebographic signs of venous damage were observed in 26%. Nearly all of these patients showed a distinct tendency to increased edema for at least two months postoperatively, but a similar postoperative reaction was found in only 20% of the remaining patients.

At follow-up examinations which were performed four to six years later, 75% of the patients who showed phlebographic signs of venous damage still suffered from edema of the leg and only 23% of the remaining patients had such edema. In the latter group, the edema was most frequently referable to persistent varices. Occlusion of the deep veins was not observed in any of the patients, and none of them showed unquestionable clinical signs of deep thrombosis. Only one patient in the control series showed similar postoperative changes. It was therefore concluded that the venous damage was caused by the sclerosing injection. Although it must be admitted that the resultant venous damage led to only a moderate intensification of the discomforts or to persistence of the preoperative discomforts in spite of the disappearance of the varicosities, this damage was, in contrast to persistent varices, incurable.

Increased Heparin Resistance After Operation.—T. Holger-Madsen and M. Schiøler (*Acta chir. scandinav.* 118:257-263, 1959- 1960) studied the plasma heparin thrombin time in the postoperative period in a series of 20 surgical patients. The principle of this test is to add heparin to platelet-poor citrated plasma and determine the clotting time with thrombin. By way of comparison, the heparin tolerance test was performed as well. The increase in heparin resistance, demonstrable postoperatively by the heparin tolerance test, was also found in the form of a shortening of the heparin thrombin time.

The items in these letters are contributed by regular correspondents in the various foreign countries.

This shortening occurred in all patients from the first to the third postoperative day, and was most marked from the third to the sixth (average fourth) day after operation. The authors commented that increased thromboplastin activity in the blood had been reported as a probable explanation of the increased heparin resistance which was determined by the heparin tolerance test. In addition to an increase in the plasma thromboplastin activity, there might, in the postoperative period, be a question of a migration of tissue thromboplastin to the blood from traumatized tissue in the operative field. Whether this was sufficient to explain the increase in heparin resistance determined by the heparin thrombin time could not be definitely stated.

GERMANY

Corticosteroids for Hemoblastoses.—H. Gerhartz of Berlin (*Ärztl. Wchnschr.* 15:7, no. 1, 1960) said that the use of ACTH and cortisone in hemoblastoses is based on the observation that these hormones administered in suitable dosage, stimulate granulopoiesis, erythropoiesis, and thrombopoiesis and effect involution of the lymphatic tissue. The catabolic effect on the nucleic protein synthesis inhibits the maturation of lymphocytes. First a relative increase in lymphoblasts occurs and this is later followed by complete disappearance of all lymphatic cell elements, while lymphocytolysis and phagocytosis of the lymphocyte rudiments occur at the same time. Cortisone therefore acts mainly on the lymphocytes and lymphopoiesis.

Continuing large doses, effecting inhibition of the lymphatic reaction, damage to the reticuloendothelial system and suppression of antibody production and mesenchymal reactions, result in a decrease in cellular and humoral defense mechanisms, and the development of bacterial infections is favored. Treatment of hemoblastosis with corticosteroids makes use of their several effects which vary greatly in relation to dose and duration of treatment. Small doses improve the subjective condition and hemorrhagic diathesis by rapidly improving capillary fragility. Large doses have a pharmacodynamic effect, especially in patients with acute leukemia. In this indication, the corticosteroids have achieved an established place beside the cytostatics and blood transfusions.

Because of myeloblastic activations, cortisone therapy is strictly contraindicated in patients with promyelocytic leukemia, chronic myelocytic leukemia, and polycythemia. Success in patients with acute leukemia depends on massive dosage; 150 to 3,000 mg. of prednisolone daily for two to three weeks is recommended. The effect occurs earlier than with cytostatics but the remissions achieved are of shorter duration. It is therefore necessary to supplement the corticosteroids in the second to third week with cytostatics and with antimetabolites in children who have acute leukemia. Cortisone should be given to adults only after the more effective cytostatics have been tried.

The effect of corticosteroid therapy is essentially symptomatic in patients with lymphadenosis, Hodgkin's disease, reticuloendothelial sarcoma, and plasmocytoma. In those with chronic lymphocytic leukemia, it is hardly possible to achieve hematological remissions or reversion of the lymph node and splenic enlargement. Important indications are intercurrent hemolytic crises and anemia with granulopenia and thrombopenia in which cytostatics cannot be given in sufficiently large doses. Corticosteroids, even in massive doses, also cannot be expected to effect reversion of the granulomas in Hodgkin's disease and reticuloendothelial sarcoma, but small doses may effect transient subjective improvement. In plasmocytoma, a dose of 30 to 60 mg. of prednisolone daily effects improvement in symptoms and skeletal pain.

Radium for Uterine Bleeding.—E. Göltner (*Medizinische*, no. 51, p. 2516, 1959) stated that intrauterine radium therapy is a simple method for treating climacteric and preclimacteric bleeding. Filtration of the radium with monel metal allows the beta rays (range 7 mm.) to pass in addition to the gamma rays. This increase in dosage effects rapid searing of the uterine mucosa, and the time necessary for treatment is shortened. The ovaries, therefore, are exposed to only 20% of the radiation dosage applied in previous treatments. The radium is applied after giving a short-acting anesthetic. After determining the length of the uterine cavity, dilation of the cervical canal, and thorough curettage, three radium carriers of different length are inserted into the uterine cavity. According to the length of the uterus, 70 to 100 mg. of monel-filtered radium remains in the uterus for four to six hours.

Recently it has become possible to introduce an egg-shaped tampon containing 10 mg. of radium into the uterine cavity. This provides more efficient radiation of the uterus. The author used this treatment in a series of 312 patients, 224 with the rod-shaped and 88 with the egg-shaped carriers. Most of the patients were between the ages of 40 and 52 years. Irradiation menolipsis was preceded by careful general examination with special attention to the hemoglobin level. The treatment was applied in younger patients only when bleedings relapsed after one or several curettements and conservative treatments were unsuccessful. The dose of monel-filtered radium depended on the size and shape of the uterine cavity. In most patients 450 to 500 mg. were used. Routine determinations in bladder and rectum showed that usually a larger quantity of gamma rays was present in these organs than with the use of platinum-iridium-filtered radium carriers.

In this series, 254 patients were studied for three months to four years after treatment. Of these, 187 had been treated with the rod-shaped and 67 with egg-shaped applicators. In addition to the immediate hemostasis, bleeding did not recur in 67% of the rod-treated and 72% of the egg-treated patients. Relapses which required further treatment occurred in 9% of the rod-applicator treated and 7% of the egg-applicator treated patients. The better results obtained with the egg-applicator method were ascribed to the fact that, with this method, the tubal corners are irradiated. Most relapses were caused by nonuniform irradiation effect. Treatment was well tolerated and only 25% of the patients reported increased leukorrhea for two to three weeks after treatment. No case of pyometra was seen. The women could usually be discharged from hospital on the fifth to seventh day after treatment.

The Counting of Thrombocytes.—Benthaus and Havenstein (*Medizinische*, no. 51, p. 2532, 1959) stated that since thrombocytes are the least stable among the formed blood elements, platelet counts differ from person to person and in any one person at various times. It is therefore of no significance to refer to average or normal thrombocyte counts or to state upper and lower limits; 200,000 to 400,000 thrombocytes per cubic millimeter can be considered sufficient generally.

The easiest method of counting, unless its margin deviates too much from the above values, is preferable in general practice to the most exacting method. The authors found direct counting in the freshly obtained citrated plasma satisfactory, without applying a stabilizer. They obtained consistent results, which compared well with those obtained by Fonio's method, in a great number of determinations. The method is used as follows: 5 cc. of citrated blood from a vein is allowed to stand at 4 C (39 F) for 1 hour and then is drawn into a leukocyte pipet to mark 1 and diluted with isotonic sodium chloride solution to mark 11. When this mixture is transferred into a counting chamber, the platelets deposit at the bottom after 10 minutes and can be clearly seen by phase-difference microscopy or normal microscopy. Counting 100 of the smallest squares proved most satisfactory. In relation to the height of the chamber and the dilution of the blood, the count was multiplied by 500.

Comparative trials showed that lower counts are obtained when sedimentation takes place at higher temperature or the time is prolonged, and these factors should therefore be controlled. Thrombocyte counts made from 30 healthy subjects by this method ranged from 220,000 to 357,000 (average 314,000). The difference from the counts obtained with Fonio's method was 70,000. The ease of this method has much to commend it for general practice.

INDIA

Nutritional Edema and Marasmus.—K. K. Kaul (*Indian J. Pediat.* 27:1 [Jan.] 1960) stated that the reason some children on a starvation diet develop nutritional edema while others show signs of marasmus is not known. Children suffering from severe malnutrition have been found to show biochemical changes. The author studied 22 children who had severe malnutrition with edema and 28 who had severe marasmic malnutrition. Only those children who weighed less than 50% of their expected weight were included in the study. Twenty normal children served as controls. Of the children with nutritional edema, 60% showed low normal to normal serum sodium levels. The potassium levels were, however, significantly low in 14 of the 22 who had edema. The calcium levels were in the low normal range, the chloride level was high normal, and the bicarbonate level showed a tendency toward low normal values.

After treatment, the results indicated a slight fall in the sodium and chloride values, a significant rise in serum potassium level, and a small rise in the bicarbonate level. There was a general tendency toward improvement in the ionogram, but most failed to reach the normal figures for serum potassium although the clinical response to high protein therapy, blood transfusions and vitamins was satisfactory. The severity of edema was not correlated to the electrolytic concentration of sodium, potassium, calcium, chloride, and bicarbonate. These patients with edema showed a tendency toward hypokalemia while a tendency to sodium retention was seen in only 40% of them, the others showed low normal to normal values. As the severity of the edema was not proportional to the increase in serum sodium, retention of sodium was apparently not responsible for the edema. Most had normal to high normal serum chloride levels. As serum sodium and chloride levels were closely linked, the high chloride values could be explained by the rise in serum sodium levels in 40% of the patients.

In the 28 children with marasmus, a tendency to low normal values for serum sodium was noticed while the serum potassium level remained in the normal range; 50% had low normal and the others had normal values for calcium; serum chloride varied from low normal to normal; and bicarbonate levels tended to be distinctly raised. A definite tendency toward alkalosis was revealed in 42%. Repeated estimations in these children after treatment showed that serum sodium, potassium, and calcium levels were not significantly affected; the serum chloride level showed a slight rise toward normal and the bicarbonate level a distinct fall towards normal. Of the patients in this series, 70% had low serum sodium level.

The severely wasted children showed a close relationship between sodium and chloride ions, the two showing parallel deviations. Although a fall in serum patassium was common in edematous malnutrition, only 21.4% of the marasmic children had low potassium values, the others had normal values. Only 25% had hypocalcemia. The low serum calcium levels might have been due to the low serum protein values as a part of blood calcium is bound with proteins, but why hypocalcemia was more common in marasmus as compared to malnutrition with edema could not be explained. Edematous malnutrition probably constitutes a later stage as compared to marasmus when the kidney has been adversely affected after repeated bouts of diarrhea and dehydration leading to retention of chloride. A fall in serum chloride level is spontaneously followed by a compensatory rise in extracellular bicarbonate, and the children with alkalosis in this group also showed hypochloremia. The clinical response in these children to dietetic and supportive measures was satisfactory, but a recheck of the ionograms showed that although there was a general tendency towards normalcy, about one-half of the patients still had hyponatremia and some had hypochloremia. Dietetic treatment by itself was therefore inadequate in regard to the electrolytic needs of the child, and serum bicarbonate levels remained high in most of the patients.

Giardiasis and Intestinal Disorders.—To study the etiological role of Giardia in intestinal disorders of childhood, A. Libov and co-workers (*Indian J. Child Hlth.* 9:217 [April] 1960) observed 180 children for a year and obtained no positive proof of its causative role in these conditions. Of the 180 children, 77 had normal stools, 35 had chronic intestinal disorders, and 68 had acute intestinal infections. The incidence of giardiasis was 35.5% on an average. Among the children with normal stools, the incidence was 24.6%; in those with acute disorders, it was 32.3%; and in children with chronic disorders, 65.7%. Among those with acute disease, Giardia was found in the active stage of the disease in only one, while in others it was seen when the infection was subsiding and the stools were not affected in any way by its presence.

Appearance of the organisms coincided with the convalescent stage. The organisms invaded the intestine weakened by infection but were not the cause of the disorder. Giardia were common in children who suffered from chronic diarrhea. Thus in a group of 29 patients, 12 had chronic diarrhea and 17 had other chronic manifestations; 27 were given specific treatment. In 26 patients, a single course of treatment eliminated the Giardia. Of these, 18 had loose stools before treatment and in 10, loose stools persisted even after eradicating the organisms. In only isolated cases did this treatment succeed in relieving abdominal pain, diarrhea, and loss of appetite. Thus persistent and prolonged intestinal dysfunction is more likely caused by lowered resistance than by the presence of Giardia, and treatment should be directed to the major cause of diarrhea and to raising the general resistance.

NORWAY

Cancer of the Prostate.—Dr. R. Andersen (*Nordis. Med.*, April 7, 1960) reported on his experience with 320 patients who had cancer of the prostate. This is the commonest form of malignant disease in man and is responsible for about 13% of all the malignancies in men. Classifying these patients histologically, he noted that carcinoma was more malignant than adenocarcinoma, showed a preference for the younger age groups, and was associated with pain in about 40% of the patients who have it. The hormone treatment given to 240 of the patients consisted usually of giving 5 mg. of diethylstilbestrol three times daily for two to three weeks, thereafter 5 mg. every evening for the rest of the patient's life. The cancer mortality was 55% for the hormone-treated patients and 66% for the men not receiving this treatment. Without it, only 9% of the untreated patients were still alive after five years, whereas this was the case with 43% of the hormone-treated patients. This treatment was equally effective whether the tumor was an adenocarcinoma or a carcinoma. Generally speaking, survival for about four years may be anticipated for the men undergoing hormone treatment, whereas without it death occurs within about two years.

Potassium Perchlorate for Thyrotoxicosis.—Since November, 1958, thyrotoxicosis has been treated at the Aker Hospital with 0.4 to 1.6 Gm. of potassium perchlorate daily. Dr. H. Klingenberg (*Tidsskr. norske laegefor.*, April 15, 1960) treated a series of 16 patients (14 women and 2 men) with this drug for an average of eight months. The effects of treatment were checked by blood cholesterol determinations, basal metabolism rates, the patient's own observations, and clinical findings including measurements of weight. Started in hospital, this treatment was continued after discharge and follow-up examinations were made monthly. All the patients reacted by a fall of the basal metabolic rate after the treatment had lasted for 1 to 10 weeks, and in 14 cases the patients became euthyroid after the treatment had lasted 4 to 22 weeks. The treatment of two patients had to be discontinued because of rashes. In one of these a generalized itching erythema developed after 600 mg. had been given daily for 20 days. The rash disappeared when the drug was discontinued and hydrocortisone was prescribed. Leukocyte counts of all 16 patients failed to reveal any sign of leukopenia.

SWEDEN

Shortage of Nurses.—Serious as the shortage of physicians is, the shortage of nurses may have played a still more important part in the life of the community last summer and autumn, if one were to judge by the closing of hospital departments. Throughout last autumn the newly erected central block of the general hospital in Lund remained empty, and in a hospital in Köping no operation could be performed after 5 p. m. for five days in the week for the same reason. Eight departments with 200 beds in the Karolinska Hospital in Stockholm were in the same predicament. Hospital architects are now being blamed for having been so prodigal in the creation of modern hospitals which require staffs of highly skilled nurses. How much more economical it would be, in this respect, to support homes for the aged and the incurably ill who can be cared for by fewer and less highly skilled attendants. The opening of two new schools of nursing last year may help to attract more girls to this calling. Wholesale appeals are being made to married nurses to work part or full time in the hospitals.

Prognosis for Alcoholics.—Under the auspices of a municipal temperance committee, courses of disulfiram were provided for several hundred alcoholics in Gothenburg. From among them, 126 were studied by a social worker who visited their homes with a questionnaire designed to throw light on the patient's past, present, and future condition. These answers were examined by Dr. C. G. Berglin (*Svenska läkartidningen*, March 11, 1960). A statistical analysis enabled him to allot so many points, good or bad, according as some given factor had a favorable or unfavorable effect on the prognosis. Thus the prognosis was down 25 points if the patient had begun to drink before the age of 21, down another 25 points if he had had more than five bouts of acute alcoholism, down 19 if he had used some substitute for alcohol such as methylated spirits, and down 40 if he was carefree when undergoing treatment.

On the other hand the prognosis was up 11 points if he was over 40 when he began to drink, up 13 if he was married, and up 20 if his temperament was equable. After the lapse of a year, 31% of the 126 had become abstinent and another 31% improved. The remaining 38% ended in relapse to a former state, with admission to some institution or other in most cases. Dr. Berglin concludes that, despite a poor prognosis, a good result is possible in some cases.

Propionylmethazine for the Sleepless and Alcoholics.—*Svenska läkartidningen* for March 18, 1960, contains two articles on propionylmethazine (propavan), which is a derivative of phenothiazine. The first is by R. Sannerstedt, who gave it for its sedative effects to 24 occupants of a geriatric hospital (16 were mentally normal and 8 had cerebral defects). The ages of the patients ranged from 58 to 93 years. The drug was given every evening for 12 to 14 days in a dose of 25 mg. and was increased to a maximum of 50 mg. in some cases. At the end of this treatment, a placebo was given for several days under the same conditions. In the next fortnight, propionylmethazine was replaced on alternate days by promethazine. In 12 patients the effect of the placebo was inferior to that of the drug and in 4 the effects of the two could not be distinguished. A good hypnotic effect was obtained in 60 to 70% of the patients taking the drug and 24% of those who took the placebo. None complained of morning drowsiness; tests of the blood, liver, and urine, while the drug was given for periods up to two months, showed no undesirable side-effects.

The second article is by R. Lindqvist who gave the drug to 200 alcoholics. A follow-up examination was made of 32 of them who were given 25 mg. of the drug two to four times a day when they were in the excited stage of alcoholism. The results were excellent in 19, good in 12, and poor in 1. The clinical effect was rapid, sometimes noticeable within the first 24 hours. Many remarked that the drug was better than others of which they had had personal experience. Minor side-effects were noticed in only two patients (slight dizziness in one and dryness of the mouth in the other). There was no evidence of accumulation or addiction.

Listeriosis.—The diagnostic awareness of a disease due to an infection with Listerella monocytogenes, type 1, probably accounts for several articles published in Sweden on this subject in the last two years. They deal for the most part with cases observed in large towns, but similar cases may soon be found in smaller communities. Most of the cases reported were in infants. The clinical findings were usually those of septicemia or meningitis, and the mortality was high. From the children's department of the central hospital in Eskilstuna, Kaijser and Malmström (*Svenska läkartidningen*, March 11, 1960) reported the case of a girl weighing 3,050 Gm. (about 7 lb.) at birth. At the age of 2 weeks she was admitted to hospital suffering from fever and general malaise. The spinal fluid contained 1,024 mg. of total protein per 100 ml., 5,300 leukocytes, mostly polymorphonuclear cells per cubic millimeter, and a few gram-positive rods. A culture sent to Professor Seeger in Bonn yielded L. monocytogenes, type 1. Treatment with various antibiotics was followed by some improvement, with return of the spinal fluid to normal, but hydrocephalus developed and the baby died at the age of 65 days. No growth of Listerella could be obtained postmortem from brain, spinal fluid, or intestines.

UNITED KINGDOM

Idiopathic Steatorrhea.—W. T. Cooke and co-workers (*Lancet* 1:933, 1960) used the peroral jejunal biopsy technique on adult patients with celiac disease or idiopathic steatorrhea. Results of histological examination of the biopsy specimen correlated with the clinical features, the hematological, radiographic and biochemical findings, and the absorption of vitamin B_{12} labeled with cobalt-60. It was concluded that at least two and probably three etiologically different disorders are responsible for idiopathic nontropical steatorrhea.

The most striking and homogeneous histological appearances were found in one group of patients. The jejunal mucosa was of normal or reduced width, the surface was completely or almost completely flattened, and no villi were present. Mild to moderate cellular infiltration, mainly with plasma cells, occurred. The intestinal glands were widely separated, and the cells of the surface epithelium were cuboidal or flattened. The histological appearances were the same in remission as in relapse. The vitamin B_{12} absorption, folic acid excretion, and xylose absorption were within normal limits. Anemia was present in only about 25%. All the patients had steatorrhea and abnormal radiographic appearances. The second group showed abnormal villi which were short, broad, and squat, and the cellular infiltration was heavier than in the first group. Folic acid and xylose excretion were impaired, and low vitamin B_{12} and iron levels were present in the serum.

Both the first and second groups gave a history of loss of weight, malaise, and diarrhea, and both responded to treatment with a gluten-free diet. Another group with symptoms of anemia and diarrhea had normal jejunal biopsies. The authors believed that, although clinically all these patients were thought to be suffering from idiopathic steatorrhea, the laboratory findings indicated that those with absent villi were etiologically distinct from the rest. These are the patients with true idiopathic steatorrhea. The second group with the abnormal villi probably represented more than one type of etiological disorder. For this group there is no satisfactory name. Many of those in the second group showed evidence of chronic inflammation and chronic jejunitis and various degrees of atrophy.

Salicylates and Hyperthyroidism.—Hetzel and co-workers (*Lancet* 1:957, 1960) showed that the administration of sodium salicylate orally to normal subjects caused a decrease in plasma protein-bound iodine (PBI) within two hours and that long continued administration of salicylates in therapeutic doses resulted in a persistently lowered plasma PBI. They also studied the effect of salicylate on the increased level of plasma PBI in hyperthyroid patients. The diagnosis was confirmed by the uptake of iodine-131, basal metabolic rate, and plasma PBI. After a preliminary observation period of three to eight days, salicylate was administered orally as the calcium salt in doses of 6 to 8 Gm. daily. It was found consistently to depress the high level of plasma PBI in these hyperthyroid patients. In both normal and hyperthyroid subjects the effect was attributed to an interference with the normal feedback mechanism, possibly situated in the hypothalamus, which controls the circulating level of thyroid hormone. There was a consistent, although significantly smaller, decreases in plasma PBI in six hypothyroid subjects after they were given salicylate and were maintained on desiccated thyroid gland. The rate of decrease in plasma PBI after the administration of salicylate closely resembled that seen after administration of iodine solution, strong, but this solution causes the sleeping pulse rate to decrease, whereas salicylate does not. This limits the possible value of salicylate in the therapy of hyperthyroidism.

New Anabolic Steroid.—Great advances have been made in separating the androgenic from the anabolic effects of substances related to testosterone. It is desirable that anabolic steroids should have minimal virilizing activity if they are used for the treatment of women and children. Foss (*Brit. M. J.* 1:1300, 1960), in short-term studies with a new anabolic steroid, methandrostenalone, showed that its nitrogen-retaining activity is five times that of norethandrolone or of methyltestosterone. The preparation was given to nine physically underdeveloped children and four women of subnormal weight or with osteoporosis. Records were kept of the weight, height, and span of the children, and roentgenograms of the epiphyses were taken.

Methandrostenalone had a powerful anabolic effect, stimulating growth and increase in weight and minimal signs of virilization. In a dose of 0.25 to 0.5 mg. per kilogram given for four to six weeks, with a resumption of treatment after three or four months, it was effective in increasing the height of stunted children from 2.5 to 4.5 in. in a year; weight was increased from 11 to 28%. The women were given 0.5 to 1.6 mg. per kilogram. This dosage produced an increase in weight without the suppression of menstruation or changes in the voice. It therefore seems that methandrostenalone in doses known to produce a good anabolic effect is free from androgenicity in women; it has minimal activity in this direction in children when the dosage given is not above 0.5 mg. per kilogram and it is given for short periods only.

Vagotomy and Duodenal Ulcer.—H. W. Burge (*Ann. Roy. Coll. Surgeons England* 26:231, 1960), discussing vagal section and chronic duodenal ulcer, con-treatment of choice in patients with deep vein thrombosis, if only because of the danger of pulmonary emboli," we feel that our patients on phenylbutazone get better faster (average hospital stay of five to seven days), are more comfortable, and have less tendency to develop chronic venous insufficiency than patients treated with anticoagulants alone. Incidentally, we have not had a single instance of pulmonary embolization in any of our patients treated with phenylbutazone, either alone or combined with an anticoagulant.

In superficial phlebitis, we have found this drug so specific that when we encounter failures we immediately try to answer the following questions. Does the patient actually have a phlebitis? Is he actually receiving the recommended dosage? Is there an occult systemic disease present, such as carcinoma, to explain the lack of response?

Irwin D. Stein, M.D.
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EPIDEMIOLOGY OF THE FUTURE

To the Editor:—I would like to take strong exception to one of the statements made in the fine editorial, "Epidemiology of the Future," in The Journal, Sept. 12, 1959, page 188. To say that "Mental illness is the only major public health problem that is not adequately reported" is to hide from the entire medical profession the critical need for morbidity reporting of several groups of illness which are of grave public health significance at the present time. Indeed, one of the greatest stumbling blocks to more rapid progress in subduing today's top killers is the inability to design a method acceptable to private practitioners which would ensure adequate reporting of these "noncommunicable" diseases. Surely the forces of preventive medicine will need to be directed against the public health problem of mental illness long years into the future; however, I would like to suggest moderation in assessing the public health problems of today.

S. D. Doff, M.D.
Florida State Board of Health
Jacksonville 1, Fla.

HOSPITALS WITHOUT AVAILABLE HOUSE STAFFS

To the Editor:—We at St. Clare's Hospital are studying the problem of how to run a 150-bed general hospital without available house staff. This problem has interested us for several years. We have been functioning, as many other hospitals have, with foreign residents, usually men who have left approved resident training programs and are awaiting citizenship. We have been unable to obtain an approved general practice residency program. Thus, we fall into the large group of hospitals with an unapproved, but active, teaching program. Because of this we have been able to have a staff of five resident physicians, but we anticipate that, because of the new examinations for foreign graduates and the decrease in the available positions from foreign countries, we may be faced with the same dilemma that many other hospitals are facing today, namely, that we will have no resident physicians, or, at the most, one or two. For this reason, I am vitally interested in obtaining data on the methods that other institutions have used to solve this problem. We have already made up a program for emergencies of this nature, but it is our hope that, by the pooling of information, solutions can be publicized that might be beneficial to many hospitals with this difficulty throughout the nation.

Monroe H. Mufson, M.D.
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NERVE CONDUCTION VELOCITY

To the Editor:—I should like to call attention to an incorrect statement in the article by Johnson and Olsen, "Clinical Value of Motor Nerve Conduction Velocity Determination," in The Journal, April 30, page 2030. On page 2034, the authors make the following statement. "Frequently it is difficult to differentiate virus encephalomyelitis from poliomyelitis. However, measuring the nerve conduction velocity provides a very useful objective method for making the diagnosis, since the conduction velocity is normal in poliomyelitis and reduced in virus encephalomyelitis."

The authors quoted one of my papers on the technique of measuring nerve conduction velocity and changes incident to traumatic damage to the nerve, but they apparently missed my subsequent work bearing directly on the sentences quoted above. I showed in a series of 26 patients that the conduction velocity in patients with poliomyelitis is indeed slower than in normal persons and, further, that the degree of slowing is directly related to the severity of the muscle weakness (Hodes, R.: *J. Neurophysiol.* 4:257-266 [July] 1949). That the reduced conduction velocity could be explained by a selective destruction of large motor horn cells and their large axons by poliomyelitis virus was suggested in another paper, in which the small size of the remaining motoneutrons in the spinal cord of monkeys previously infected with poliomyelitis was related to the severity of the lesion (Hodes, R.; Peacock, S. M., Jr.; and Bodian, D.: *J. Neuropath. & Exper. Neurol.* 8:400-410 [Oct.] 1949).

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BOOK REVIEWS

Practical Neurological Diagnosis: With Special Reference to the Problems of Neurosurgery. By R. Glen Spurling, M.D., Professor of Neurosurgery, University of Louisville School of Medicine, Louisville, Kentucky. Sixth edition. Cloth. $6.75. Pp. 284, with 70 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

The appearance of the sixth edition of this monograph on neurological diagnosis attests to its popularity as a text for students and resident house officers. The author has followed, in general, the form of the original edition which was published in 1932. He has however eliminated the chapters contained in the previous editions which dealt with radiological diagnosis because he believed that these obscured his original intent and added extensively to the size and cost of the volume. His approach to the diagnosis of neurological disease is that of his specialty, neurosurgery, and is based on his extensive experience in this field since the time of his training with Dr. Harvey Cushing over 30 years ago. There is a chapter on history taking and general physical examination and one on the examination of the cerebrospinal fluid. The remainder of the book is devoted to a discussion of anatomy and physiology of the nervous system as these apply to the diagnosis of diseases of the nervous system. The various portions of the nervous system are considered on a regional basis, that is, cranial nerves, cerebrum, cerebellum, spinal cord, and the like.

The book is well printed. There are 70 pertinent figures which are well reproduced, 5 tables, a glossary of terms, and an index. The monograph should be of value to medical students and house officers as a guide to the anatomy and physiology of the nervous system and as an aid in localization of lesions within the nervous system. It suffers from a defect common to all short books in that it is not possible to cover all of the essential aspects of these subjects in the space allotted.

H. Houston Merritt, M.D.

Ciba Foundation Tenth Anniversary Symposium on Significant Trends in Medical Research. Editors for Ciba Foundation: G. E. W. Wolstenholme, *O.B.E.*, M.A., M.B., M.R.C.P., Cecilia M. O'Connor, B.Sc., and Maeve O'Connor, B.A. Cloth. $9.50. Pp. 356, with 41 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W. 1, England, 1959.

The preface of this book explains that it is the 50th major volume published for the Ciba Foundation and that it contains the transactions of a special symposium arranged in celebration of the opening of the foundation by Sir Henry Dale in 1949. It contains 13 papers on the status of basic medical problems, such as molecular structure in relation to biology and medicine, medical aspects of genetics, advances in general neurophysiology, the nature and action of hormones, the nature and mechanism of malignant transformation, research in chronic pulmonary disease, research in clinical nutrition, and the quantitative approach to disease as exemplified by essential hypertension. Each contribution is illustrated by tabular or diagrammatic material when necessary and is concluded with discussion of the particular points that have been raised and with a bibliography. The volume ends with a general discussion, closing remarks by the chairman (Sir Harold Himsworth), an author index, and a subject index.

This is a meaty book, filled with substantial detail and rendered especially significant by the greatness of the men who have contributed to it. It has not been allowed to run down into the introverted obscurity that sometimes spoils symposiums in which specialists talk only to each other. The editors and printers have done a faultless job. It is highly recommended to readers who have the time and patience for serious probing into some fundamental problems of medical science.

F. T. Jung, M.D.

Einführung in die stereotaktischen Operationen mit einem Atlas des menschlichen Gehirns. Introduction to Stereotaxis with an Atlas of the Human Brain. In drei Bänden. Band I: Text. Band II: Tafel 1-57. Band III: Tafel 58-76. Herausgegeben von Georges Schaltenbrand und Percival Bailey. Unter Mitarbeit von K. Akert et al. [In German and English. Volumes II and III are loose-leaf. Size 30 x 40 cm. Publication subsidized by Research Society for Cerebral Palsy, Chicago.] Cloth. $233.35; 980 marks. Volume I, pp. 493, with 230 illustrations; volumes II and III, no pagination. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany, 1959.

The editors, realizing the great potentialities of stereotaxis in brain surgery, are confronted with the problem of its "blindness" and its inaccuracies. One wonders if, when they began this study, they were aware of the magnitude of the task of giving this method much better credentials as far as its use on the human brain is concerned. The problems they encountered and their methods of solving them are clearly and interestingly portrayed. The inability to use as planes of reference those found adequate in animal experiments led them to use reference points specific to the brain itself and visible in the ventriculogram. Since the ventricular system is the chief landmark of orientation, the editors have presented a careful study as to the extent of the normal, as well as the pathologically deformed ventricular system. In order to use the ventriculogram for direct dimensional measurements, they have developed a roentgenographic technique that avoids photographic distortion. Even this refinement in technique may at times fail. To give some value to estimations, a comparative study of the size of the ventricle to the dimension of the skull is presented.

From the viewpoint of technique there are descriptions of the various stereotaxic instruments. The procedures used in various clinics are discussed in detail. This includes that of one of the editors and illustrates the role of the anatomic atlas in locating the target. The scope of stereotaxic surgery is outlined. There is also a critical evaluation of this procedure in relation to disturbances of the extrapyramidal tract system. The anatomic work is based on a study of specimens (brains) so prepared as to preserve as far as possible the relationship present in the living organ. The brains were sectioned along a system of planes developed by the authors.

Volume 2 depicts, on loose leaves, plates from these sections in gross and microscopic preparations. The laterality of the plates correspond to an anteroposterior roentgenogram. Each plate is marked with direction and distance in millimeters from zero point of the plane of section. Attached cover transparencies show the variations in size and structure as observed in a number of specimens. Loose transparencies show the maximum extent of the ventricules for the corresponding plate. These can be transposed on the ventriculogram or on the plate and show relationship of the structures.

Volume 3 shows Nissl preparations of sections through deeper nuclear structures. These are in a magnification of 20 to show the relationship of the cellular constellations.

Through authoritative scholars, they have presented in the text reviews or symposiums that afford the surgeon the results of years of study. Here is an objective presentation of present conceptions regarding anatomy, neural connections, physiology, pathophysiology, and effects of electrostimulation and electroencephalography of the structures related to stereotaxis.

This is a timely and much needed contribution to this facet of neurosurgery. Time and experience will decide its role in the development of greater accuracy of the stereotaxic instrument. The anatomic atlas will endure because of the exactness of its preparation. The anatomic and physiological presentations portray a true picture of the concepts of this time. Even though these concepts may change, this in no way detracts from their value. This material should stimulate the experienced surgeon, endow him with greater judgment, and equip him better to foresee the repercussions of his surgical acts. It should increase his ability to assess objectively and critically the value and meaning of his results and those of others. It should have a sobering influence on the tendency to accept prematurely the clinical results as they are reported.

LOREN W. AVERY, M.D.

Spiritual Therapy: How the Physician, Psychiatrist and Minister Collaborate in Healing. By Richard K. Young and Albert L. Meiburg. Cloth. $3.50. Pp. 184. Harper & Brothers, 49 E. 33rd St., New York 16, 1960.

This little book has a remarkable history. A paper by Drs. Richard K. Young and Benjamin S. Patrick, "Outpatient Pastoral Counseling in a Medical Center," was published in THE JOURNAL on September 6, 1958. Mr. Clarence Hall, senior editor of the *Reader's Digest*, was so impressed with it that he made two visits to the North Carolina Baptist Hospital, the teaching hospital of the Bowman Gray School of Medicine, to collect material for an article on the work of Chaplain Dick Young and his associates in the department of pastoral care. In order to justify the length of the article, he published it in the Book Section of the *Reader's Digest* as "condensed form of a forthcoming book" and extracted a promise from Dr. Young that he would write the book thus condensed. "Spiritual Therapy" is the result.

The book shows a new approach to the relation between physician and pastor in treatment. It is based on the treatment of patients seen in the North Carolina Baptist Hospital. The effectiveness of the combined efforts of physician and pastor is shown in patients with the following conditions: heart disease, ulcerative colitis, asthma, skin diseases, migraine, anxiety and conversion reaction, surgery, childbirth, the involutional period, and bereavement. A final chapter is devoted to the general hospital as a setting for spiritual therapy. Every chapter was read critically for medical accuracy by a Bowman Gray faculty member who is an authority in the condition discussed. The final chapter was read by Mr. Reid Holmes, administrator of North Carolina Baptist Hospital.

The foreword by Dr. David Cayer, a professor of gastroenterology, and an introduction by Mr. Clarence Hall add to the value of the book. The cases discussed illustrate how helpful proper teamwork between the physician and the minister is to the patient. The authors disdain the methods of the "faith healer" but emphasize the importance of bringing up to date Plato's view that the whole man and not the part must be treated. The book's common sense down-to-earth discussion of the sort of every day problems that are common meeting grounds should make the book of interest to physicians, pastors, and even to patients. The authors deserve commendation for an excellent job.

JOHN H. TALBOTT, M.D.

QUESTIONS AND ANSWERS

EMERGENCY MANAGEMENT OF DROWNING VICTIM

To THE EDITOR:—*There is a difference of opinion regarding the best medical management of persons who have drowned. Most doctors in this area think that the emergency is best handled by trained resuscitating crews. Such crews are available from the local fire departments, and the goal ought to be rapid transportation of the victim to the hospital, resuscitating efforts being continued in the ambulance or other emergency vehicle. In addition, anesthesiologists, a well-equipped hospital, and many qualified physicians are available. The suggested procedure assures that the patient will be treated by those best trained in immediate first-aid and resuscitation, with the shortest possible time lapse between the accident and arrival at the hospital where definitive treatment can best be given.*

Some of the emergency personnel think that, since the first-aid manuals call for medical attention at the scene of the accident, the better procedure would be to have a doctor come to the scene, so that the patient can be treated under the physician's direction. Would you obtain comments on the treatment of these patients?

M.D., Washington.

ANSWER.—Persons who suffer asphyxia or apnea, regardless of cause, require large amounts of air to be transferred rapidly in the first few seconds for successful revival. In cases of drowning, laryngospasm is likely to occur. It is important that the person who reaches the victim first knows how to obtain a patent airway and move large quantities of air in and out of the victim. No time should be lost getting the patient into the hands of a qualified anesthetist or anesthesiologist, since they have the requisite equipment to counteract laryngospasm which otherwise would probably cause the patient's death.

If the current mouth-to-mouth method of artificial respiration with hyperextension of the head and neck and forward displacement of the mandible is achieved, air should pass freely into and out of the patient's lungs. Those who have swallowed quantities of water will undoubtedly regurgitate it, because of the pressure exerted by part of the air that is going into the esophagus. The rescuer should be prepared to turn the head quickly to the side and clean out the pharynx before resuming the efforts to restore breathing. Since one does not require a "platform" to carry out the oral method, the patient should be transported as soon as possible to the nearest medical facility.

PALMAR ERYTHEMA

To THE EDITOR:—*Please discuss palmar erythema; its significance, its treatment, the influence of dyshidrosis and of estrogens, and palmar erythema as "hepatic sign."*

G. Walter de la Motte, M.D., Columbus, Ohio.

ANSWER.—Palmar erythema may be caused by many factors. Some are endocrine in nature. For example, the condition occurs occasionally during pregnancy. Excess of estrogens is held responsible for such instances. Diabetics may show the same type of erythema. It frequently is observed in patients with cirrhosis of the liver. Erythema of the palms, soles, or both may occur as an inherited trait in siblings of families in which palmar and plantar keratoma is hereditary. In patients of this category the erythema may be combined with keratoderma, hyperhidrosis, or both. Another, entirely different condition is sometimes referred to as "hereditary palmar erythema." It is nevoid in character and apparently due to teleangiectasis. The treatment of palmar erythema depends on the particular type present and the associated systemic manifestations. Therapeutic efforts in members of families with inherited keratoma plantare are at best palliative in nature.

SCALING OF THE TEETH

To THE EDITOR:—*Can scaling of the teeth do any damage to the cementum or the periodontal membrane? I have the impression that in a vigorous scaling, dentists scale below the neck of the tooth, especially if the root is exposed. Some of my patients have had to have teeth extracted because of a cavity that extended from a part of the root into the pulp chamber. Some of these patients give a history of many or vigorous scalings.*

M.D., West Virginia.

ANSWER.—Scaling of the teeth is damaging to the cementum only if the instrument (scaler) is used incorrectly or in excess. The purpose of scaling a tooth, both the crown and the root, is to remove all calcified accretions from the dental surface, thus eliminating a source of mechanical irritation to the adjacent soft tissue. The cemental surface of the root is often found to be an irregular surface and, in such cases, there is the intentional planing of the

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

root surface with an instrument called a periodontal curette. In such cases, cementum is removed in minute amounts until the dental surface is smooth and no longer a source of irritation to the gingival tissues.

It is not likely that scaling of the teeth would be injurious to the periodontal membrane, since the area of scaling is remote from the site of the tooth-bone attachment. One objective of tooth scaling is to minimize or eliminate chronic inflammation from within the gingival tissues. This inflammation would ultimately spread to involve the periodontal membrane if the original site of gingival inflammation was allowed to persist. It is possible that the cases described of "a cavity extending from a part of the root into the pulp chamber" may be cases of dental erosion. Such a loss of tooth structure occurs independently of any root scaling or curettage.

ANEMIA AFTER THYROIDECTOMY

To THE EDITOR:—*How should anemia due to hypothyroidism after thyroidectomy be treated?*

C. D. Baird, M.D., Eureka, Kan.

ANSWER.—The anemia of hypothyroidism, either postsurgical or spontaneous, is usually of a normocytic normochromic type, although it may be macrocytic. It responds completely to oral administration of desiccated thyroid. Improvement may be slow, sometimes requiring from six months to one year for full correction. Hypochromia may be present and is thought to be the result of poor iron absorption, secondary to gastric achlorhydria. If hypochromia is prominent, iron therapy may be needed in addition to desiccated thyroid. Patients with true pernicious anemia in association with hypothyroidism have been described, and they should be given vitamin B_{12}. Failure of anemia to respond to desiccated thyroid therapy requires careful search for other factors which may be responsible for refractoriness.

LIQUID PROPANE

To THE EDITOR:—*I am interested in the toxic properties of liquid propane which is sold for heating purposes. I have recently encountered a claim of bronchitis due to inhalation of propane gas.*

E. J. Drouillard, M.D., Missoula, Mont.

ANSWER.—There are apparently no ill-effects from remaining for several hours in an atmosphere containing this gas in concentrations as high as 3 to 5% or from repeated exposures, but the combustion of this hydrocarbon with an inadequate supply of air will lead to the formation of carbon monoxide and risk of asphyxia. When used for heating purposes, combustion of the gas to carbon dioxide and water is usually complete. If, however, the supply of gas is turned down until one or more of the burners may go out or be easily blown out, while some of the other burners continue to burn, the gas from the unlit burners may undergo a flameless and incomplete combustion and produce dangerous amounts of aldehydes and carbon monoxide.

HYDROPS FETALIS

To THE EDITOR:—*What is the most recent treatment for hydrops fetalis?*

L. W. Holland, M.D., Chamberlain, S. D.

ANSWER.—Early exchange transfusion has been successful in the most severe cases of erythroblastosis, and delivery of the baby early by obstetric planning apparently causes some avoidance of the situation, though this is a disputed point. There is no immediate new hope. The only hope we can conceive of is to find some agent which would allow bilirubin early in life to be conjugated with some other substance which will make it more readily excretable and less readily diffusable into the brain. Various research attempts toward this have been made but none is yet successful. The greatest present hope for success in treatment lies in early planning for such a condition, premature delivery, and early and often multiple exchange transfusions.

GASOLINE SNIFFING

To THE EDITOR:—*I currently have a 17-year-old boy under investigation for addiction to inhalation of gasoline fumes. This boy has been inhaling gasoline fumes since he was a small child. What physiological changes are produced by the inhalation of gasoline and how toxic are the fumes?*

R. V. Edwards, M.D., Crookston, Minn.

ANSWER.—Inhalation of high concentrations of gasoline may cause sudden loss of consciousness, coma, or even death. Lower concentrations may produce flushing of the face, followed by staggering gait, mental confusion, disorientation, ataxia, blurred speech, and difficulties in swallowing—a typical jag. After continued or repeated exposure to fairly high concentrations (chronic gasoline poisoning), the patient may lose his appetite and lose weight. He may look pale and suffer from nausea, headache, nervousness, neurasthenic manifestations, muscular weakness, and cramps. He may become dull and listless, lose his memory, become confused, suffer from analgesia, paresthesias, and myalgia, and may develop polyneuritis and anemia.

Persons vary greatly in their susceptibility to petroleum vapors not containing other poisonous components. About 0.3% of gasoline vapor in air will make a man dizzy in about 15 minutes. A man accustomed to breathing the vapors can endure larger percentages, but 1 to 2% of gasoline vapor will make most men dizzy in three to five minutes, and this percentage will endanger life if exposure is continued for one hour or more.

PLASTIC CEMENT FUMES

To THE EDITOR:—*I have recently seen a teen-age boy who has become addicted to sniffing the fumes from plastic cement. I have heard that this practice has been encountered in the Los Angeles area. What are the pharmacology and toxicology of such products?*

Joseph F. Rorke, M.D., Scottsdale, Ariz.

ANSWER.—Solvent vapors are inhaled to induce an experience of fantasy in which pleasurable hallucinosis is prominent. Model airplane enthusiasts have been warned about the serious consequences of inhaling vapors from certain types of glue. It is impossible to assess the toxicity of a product without knowing the approximate concentration of the potentially toxic substances used in the formulation. Solvents in general are primarily narcotic agents. Sporadic reports of "jag" effects are based on the initial stimulant effect of these substances.

Chlorinated hydrocarbon solvents, such as carbon tetrachloride, chloroform, and trichloroethylene, are sometimes used in the plastic cements. The practice of sniffing the fumes of this type of solvent have been reported occasionally from industry and it was inevitable that the more imaginative of our teen-agers would also discover the exhilarating and intoxicating properties of these solvents. These materials are liver poisons, and the frequent inhalation of concentrations sufficient to cause a jag are decidedly harmful to this organ and may cause severe damage to the respiratory and circulatory systems.

VAGINAL HYSTERECTOMY

To THE EDITOR:—*Having performed hysterectomy through the vagina, does one then tie the two stumps to each other? Is the incidence of postoperative prolapse of an oviduct, with subsequent strangulation necessitating an emergency operation, less common when the two stumps are tied together?*

Fuad S. Schoucair, M.D.,
Kamischlie, Syria, U. A. R.

ANSWER.—There are few operations that have as many variations as vaginal hysterectomy. Various textbooks on operative gynecology and published reports in their outline of the operation all suggest that it should eliminate, so far as possible, the complication mentioned. Postoperative prolapse of the oviduct is encountered on rare occasions but is seldom possible if the pelvic peritoneum is carefully closed. We have never had strangulation of the oviduct as a postoperative complication and would suspect that, if it occurred, it would result from misplacement of a suture. One of the happy possibilities in the operation is the opportunity to use the stumps of the broad, cardinal, and uterosacral ligaments to further the correction of anterior and posterior relaxation and vaginal prolapse. Since most of the results that are reported are favorable, it probably does not matter how or where they are secured, provided their presence serves the useful purpose of support or prophylaxis. If the vaginal closure, from peritoneum to vaginal mucosa, is performed in an orderly fashion, there is little opportunity for the oviduct to prolapse.

MENTAL RETARDATION

To THE EDITOR:—*A mother and father of high intelligence have five children. The first four children also are highly intelligent. The fifth child, now in the third grade, has an intelligence much below the average of those in her class in school. Before the birth of the last child the mother had a severe hemorrhage which, her obstetrician told her, was due to a premature separation of the placenta. The child was born on schedule seven days later. This child also has some difficulty with finer movements of the hands as in writing, but is well coordinated in coarser movements as in swimming and skiing. The delivery was normal. The parents wish to know if the separation could have produced enough cerebral anoxia to account for the lower mentality of the child.*

M. A. Shillington, M.D., Fort Lauderdale, Fla.

ANSWER.—It is possible that the hemorrhage resulting from the placental separation resulted in sufficient cerebral anoxia to account for the mental condition of the child. In evaluating the maternal hemorrhage as a possible factor in the etiology of the mental retardation, it would have helped to know the amount of blood lost, the duration of the bleeding, and whether the fetus exhibited any signs of cerebral anoxia, such as increased activity at the time of the placental separation. In view of the frequency of the birth of mentally retarded children, it is also possible that the retardation of the child arose from a cause in no way related to the maternal bleeding.

SODIUM CACODYLATE

To THE EDITOR:—*I have been giving 50 mg. of sodium cacodylate intramuscularly twice a week to a patient with psoriasis. How long can I give two injections a week without causing harm to the patient?*

M.D., Indiana.

ANSWER.—The official (N. F.) dose of sodium cacodylate injection is 0.3 Gm., which is much more than the dosage you are currently giving. The drug is slowly decomposed in the tissues into trivalent arsenic. The action is thus more gradual and less toxic than that of other arsenic compounds, but it is not easily controlled and is therefore undesirable. It was formerly used in the treatment of anemia, leukemia, and certain skin diseases but has been supplanted by more effective remedies. Psoriasis responds best to the external application of mercurial or tar preparations.

HIRSUTISM

To the Editor:—*Is the removal of excess hair from the lower extremities by electrolysis harmful to the skin or other tissue in a 14-year-old girl?*

M.D., New York.

Answer.—When executed by a skilled and careful technician, electrolysis is not harmful and regrowth in treated hair follicles will be minimal, but even under the best circumstances, the treatments are so tedious, uncomfortable, and expensive that few persons persist until large areas are permanently denuded. In spite of these disadvantages, individual differences in the degree of motivation and discomfort experienced are so great that electrolysis should not be ruled out even though it may seem impractical for the average person with extensive hirsutism.

ALCOHOLIC BEVERAGES AND ORALLY GIVEN HYPOGLYCEMIC DRUGS

To the Editor:—*In your reply to the question about alcoholic beverages and orally given hypoglycemic drugs which appeared in* The Journal, *May 7, page 128, no therapeutic recommendation is made other than "abstinence from either alcohol or sulfonylurea compounds." The purple-red flushing of the skin, an occasional complication of oral diabetic treatment, is more embarrassing to observers than distressing to the patient. In my experience, the administration of any orally given antihistaminic drug at least one hour prior to drinking alcoholic beverages will usually prevent this in such sensitive persons who are using sulfonylurea compounds.*

Henry Dolger, M.D.
1049 Park Avenue
New York.

PROPER USE OF POSTAL SERVICES

To the Editor:—*The answer to the query on proper use of postal services in* The Journal, *Jan. 2, page 118, was poorly done. (Is it legal for a physician certified for medical practice in one state to send medicine or prescriptions, or both, to a patient in another state?) Why did your consultant not state which federal regulation is involved? If there is none, say so. I think this answer is about the laziest opinion I have read in a professional journal for some time.*

Elvin D. Thompson, M.D.
Box 167
Jefferson, Iowa.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*The only federal law I am aware of in relation to this question limits "the transfer in the mails of poisonous drugs and medicines" from a manufacturer or dealer to licensed physicians and other specified individuals (18 U. S. C. A. 1716).*

A doctor is skating on thin ice when he prescribes without seeing or examining the patient, but this is true irrespective of where the physician and patient may be located.

The basic definition of the practice of medicine in state statutes provides that a person practices medicine who (a) examines or diagnoses for a fee or compensation of any kind or (b) prescribes, advises, recommends, administers, or dispenses for a fee of any kind, direct or indirect, a drug, of medicament, or appliance for the cure or relief of a wound, fracture or bodily injury, infirmity, or disease. Thus, as long as a physician engages in these activities in a state where he is licensed, he should not fear being prosecuted for practicing without a license even though his patients live outside the state.

ARTIFICIAL INSEMINATION

To the Editor:—*In* The Journal, *April 2, page 1576, there is a question regarding frozen sperms for artificial insemination. The answer stated that no reports had appeared on the subject. May I give the following reference which is one of several on the subject: Bunge and Sherman* (Fertil. & Steril. *5:193 [March-April] 1954).*

Melvin R. Cohen, M.D.
30 N. Michigan Ave.
Chicago 2.

To the Editor:—*In* The Journal, *April 2, page 1576, there is a query concerning artificial insemination. Dr. Lillian Wong should be informed that studies by Bunge and Sherman, of the Department of Obstetrics and Gynecology at the University of Iowa, have been published.*

Irving F. Stein Sr., M.D.
111 N. Wabash Ave.
Chicago 2.

The above comments were referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*Your respondent has indeed erred in stating that no reports on the use of frozen semen in human subjects have appeared in the literature. A few isolated instances of pregnancy after insemination with thawed semen have been reported. However, most of the investigation with freezing of human semen has concerned itself with improvement of the technique of freezing. Most of the clinical application, encompassing unsuccessful inseminations with ejaculates of reduced sperm concentration, remains unpublished.*

ABSTRACTS FROM THE LITERATURE

Archives of Dermatology

82:1-91 (July) 1960

Flat Cutaneous Xanthomatosis
W. K. Stewart and O. A. Finn ....p. 1
Liquid Nitrogen in the Treatment of Skin Lesions
A. F. Hall ....p. 9
Cholinesterases in Pigmented Tumors of the Skin
R. K. Winkelmann ....p. 17
Factors Determining the Skin-Drug-Vehicle Relationship
J. B. Shelmire Jr. ....p. 24
Pathogenesis of Cutaneous Myxedema
G. Asboe-Hansen ....p. 32
Solitary Trichoepithelioma
I. Zeligman ....p. 35
Giant Condylomata Acuminata of Buschke and Lowenstein
G. F. Machacek and D. R. Weakley ....p. 41
Role of Dermal Sensitivity in Ragweed Contact Dermatitis
S. Epstein ....p. 48
Histopathology of Drug Eruptions
M. L. Matte, H. Winer, and E. T. Wright ....p. 56
Norwegian Scabies
H. C. Maguire Jr. and others ....p. 62
Sarcoid Granulomas and Intradermal Tuberculin in Human Skin
H. J. Hurley and W. B. Shelley ....p. 65
Bechet's Disease as a Multiple Symptom Complex
C. Berlin ....p. 73
Inside X-Ray
P. M. Crossland ....p. 80
Report: Reunión Anual Internacional de Dermatología, Buenos Aires
M. J. Costeilo and G. C. Andrews ....p. 90

Flat Cutaneous Xanthomatosis.—Xanthomas are traditionally divided into normocholesterolemic and hypercholesterolemic forms. The tendency is to group all normocholesterolemic forms within a broadened concept of Hand-Schüller-Christian syndrome, as "Histiocytosis X". The justification for this in some of the rarer xanthomas is doubtful. Attention was drawn to an apparently benign flat cutaneous xanthoma which had been recorded only 3 times previously. An additional case is reported in a 20 year old eunuchoid male with presumed rheumatic heart disease. The xanthomas appeared during infancy. Analysis of a lesion showed a moderate generalized increase of free and esterified cholesterol, lanosterol, and nonsterol lipids. The authors consider that current classifications excessively emphasize serum cholesterol level. They suggest that analysis of lesions by the newer methods for lipids, including gas-liquid chromatography must lead to better understanding of these states.

Liquid Nitrogen and Treatment of Skin Lesions.—In this study, the local application of liquid nitrogen was found to be a superior form of treatment for such skin lesions as are characterized by abundant keratinization, scanty vascularity such as verrucae of all types, solar and seborrheic keratoses, molluscum contagiosum, and small hypertrophic scars of recent origin. This modality was disappointing or totally ineffective, however, in the treatment of vascular or cellular nevi. The outstanding advantage of the liquified gas refrigerants in the treatment of appropriate lesions lies in their extremely low temperatures (much lower than that of solid carbon dioxide) which are capable of freezing the keratotic portion of a lesion without the necessity of physical pressure, thereby obviating scarring which would result from expressing the blood from the underlying capillary bed, with consequent freezing below the dermal-epidermal junction.

Cholinesterases in Pigmented Tumors of Skin.—Butyryl cholinesterase activity has been found in some pigmented tumors. This reactivity is associated with certain dermal cells of nevi and is demonstrated most intensely in neuroepithelial nevi. There is no relation to junctional tissue, melanoma cells or blue nevus cells. The reaction is not anatomically associated with the reaction in dermal nerve networks or other structures. In general, an inverse relationship to pigmentation and to malignant potential has been observed. It seems useful to use this reaction to define a benign, papillomatous nevus appearing late in life which is nonspecific cholinesterase positive.

Factors Determining Skin-Drug-Vehicle Relationship.—This paper presents a review of recent finding in the fields of cutaneous physiology and pharmocology that relate to topical therapy, discussed primarily from a functional standpoint. The factors affecting the equilibrium between the normal epidermis and various types of vehicles were considered, as well as the effect of this physico-dynamic relationship on drug diffusion and penetration. The condition of the stratum corneum was found to be of prime importance in selection of the therapeutic modality. Certain problems in this field of investigation were defined and approaches to these suggested.

Pathogenesis of Cutaneous Myxedema.—The thyrotrophic hormone stimulates cellular synthesis and release of acid mucopolysaccharides, including hyaluronic acid, which is strongly water-binding. Increased capillary permeability and extracellular edema brings about a release of hyaluronic acid changing the water into a mucinous substance. In hypothyroidism, thyrotrophin activity is increased but is not, or is less, inhibited by thyroid hormone. In thyrotrophin-stimulated organisms, as a response to extracellular edema, excessive amounts of mucopolysaccharide come from the intracellular to the extracellular compartment forming a ground-substance gel. Moreover, fat is mobilized and replaced by a mucinous substance. The result is dermal myxedema. Circumscribed, pretibial myxedema presents excessive myxedematous issue changes. The edema due to venous stasis of the lower legs may be of primary pathogenetic significance to this disease occurring in individuals under marked thyrotrophin stimulation.

Solitary Trichoepithelioma.—Though the multiple disseminated variety of trichoepithelioma is well recognized, solitary trichoepithelioma is not so well known. Four patients with the solitary variety of trichoepithelioma were described. Three of them had similar clinical findings with a single round annular normal-colored shiny papule or nodule on the face. The other had a single nonannular papule on the face. Microscopic examination of biopsy specimens was necessary for final diagnosis. The lesions first appeared at 28, 17, 16, and 9 years of age, respectively. Clinically, solitary trichoepithelioma must be differentiated particularly from granuloma annulare, intradermal nevus, and basal cell carcinoma. Microscopically the important differential is basal cell carcinoma differentiating toward hair follicles.

Condylomata Acuminata of Buschke and Lowenstein.—The purpose of this report is to stress the fact that these uncommon lesions differ from typical condylomata acuminata clinically, histologically, and in their response to podophyllin therapy. All reported cases have occurred on the penis in adult patients. The giant condylomata typically are circular, elevated, hyperkeratotic plaques. Clinical differentiation from epithelioma of the penis is impossible. On microscopic examination, massive acanthosis with compression of the underlying structures is seen. Invasion of nerves, lymphatics, or blood vessels does not occur. Podophyllin therapy is ineffective; the preferred treatment is electrosurgery. Unequivocal differentiation from epithelioma can only be made by microscopic study of biopsy material. Application of podophyllin up to 5 weeks prior to biopsy results in abnormal mitoses and other histological changes which closely resemble those seen in squamous cell epitheliomas of the penis.

Dermal Sensitivity in Ragweed Contact Dermatitis.—Dermal delayed (tuberculin-type) sensitivity often can be demonstrated in ragweed contact dermatitis by intradermal tests with diluted extracts of the oleoresin fraction. The papular response to patch tests, which is encountered more often than a vesicular reaction, indicates that dermal sensitivity is probably the main, and at times, the only form of contact sensitivity responsible for the dermatitis. This dermal sensitivity probably accounts for some of the clinical characteristics of ragweed contact dermatitis and its prolonged course Out of 16 patients suffering from ragweed contact dermatitis and tested both with patch and intradermal tests with ragweed oil solutions of suspensions, 11 gave positive reactions to the intradermal tests, 3 gave questionable reactions, and 2 gave negative ones. One patient of this series also showed a photocontact sensitivity to the ragweed oil.

Histopathology of Drug Eruptions.—The histopathology of drug eruptions was studied in an attempt to find specific changes which would be of diagnostic value. Biopsy specimens were examined from 206 patients with cutaneous eruptions due to a variety of medications, the most common being penicillin, barbiturates, and sulfonamides. The primary pathology was located in the upper half of the dermis and consisted of a lymphocytic perivascular infiltrate, protrusion of the endothelial cells into the lumen of the vessels, hyalinization of the vessel walls, subepidermal edema, and dropping off of melanin from the basal layer into the dermis. Epidermal changes were not remarkable except for mild spongiosis and colloquative degeneration in severe vesiculobullous reactions. The lymphocyte was the most frequently encountered inflammatory cell. The eosinophil was occasionally present but was usually not perivascular in location.

Norwegian Scabies.—Four cases of Norwegian scabies in male mongoloids were found at an institution for mental defectives. Until cured these cases of Norwegian scabies seeded many cases of ordinary scabies at the institution. Norwegian scabies is a rare variant of ordinary scabies in which areas of the skin become hyperkeratotic and infested with hundreds of thousands of scabetic mites. Finding the mite in the scale from a clinically involved area is easy and confirms the diagnosis immediately. Norwegian scabies seeks out the patient already debilitated by mental or neurological disease; it is moderately contagious and responds to intensive treatment with the usual scabecides.

Sarcoid Granulomas and Intradermal Tuberculin.—This study concerned the persistent granulomatous reactions that are occasionally seen at tuberculin (PPD) skin test sites in human skin. Of 50 healthy adult Negro volunteers given 1st strength PPD skin tests, 36 reacted positively and 14 negatively at 48 hours. Five of the positive reactors developed a late, clinically evident papular response at the PPD test sites persisting through 4 to 6 weeks. On biopsy, these lesions were epithelioid granulomas, sarcoid or tuberculoid in type. The reaction could not be correlated with intensity of the 48 hour reactions. Increasing the concentration of PPD did not promote the granulomatous reactions in those who failed to develop granulomas, despite more intense 48 hour tuberculin responses with the stronger concentrations. The view is presented that these tuberculin skin tests granulomas may well be the result of a special type of allergic hypersensitivity to PPD analogous to that of zirconium and other sarcoid granulomas.

Bechet's Disease as a Multiple Symptom Complex.—According to the literature and our 10 cases, Behcet's disease appears as multiple manifestations, exhibiting vascular changes of allergic, inflammatory, or ulcerative character. It may involve the skin, predominantly of the genital region, the mouth, the eyes, the joints, the brain, and the viscera. The peculiar reactivity of the skin to intradermal saline injection, and even to a needle puncture, is of diagnostic value. The course is latent or active. The active course is characterized by acute episodes of various symptoms recurring singly or simultaneously, at irregular, frequent, or infrequent intervals. The prognosis depends on the organs affected. The involvement of the brain may cause death, of the eyes visual impairment or blindness. On the other hand, a mild course may be encountered, with attacks occuring infrequently, and eventuating in an apparent cure.

American Journal of Diseases of Children

100:7-116 (July) 1960

Observations on Acute Bronchiolitis in Infants
S. H. Wood Sell ....p. 7
Pneumonitis Induced by Experimental Infection with H. Influenzae
S. H. Wood Sell ....p. 16
Aspirin and Salicylamide Suspension in Pediatrics
M. P. Borovsky ....p. 23
Hirsutism in Adolescent Girls
A. B. Hayles and others ....p. 31
Menghini Needle Biopsy of the Liver
R. Hong and W. K. Schubert ....p. 42
Diagnosis of Neonatal Jaundice by Patterns of Serum Transaminase
S. Kove, R. Perry, and F. Wróblewski ....p. 47
Galactosemia
S. P. Dawson, R. O. Hickman, and V. C. Kelley ....p. 69
Aerobic Bacterial Flora of *Throat in Children Given* Antibiotics
J. H. Priest, A. J. Simon, and M. H. Lepper ....p. 74
Studies in Sickle-Cell Anemia
R. B. Scott and A. D. Ferguson ....p. 85
Indirect Effect of Irradiation on Embryonic Development:
I. Irradiation of the Mother While Shielding Embryonic Site
R. L. Brent and M. M. McLaughlin ....p. 94
II. Irradiation of the Placenta
R. L. Brent ....p. 103
Chondrodystrophia Congenita Punctate
M. Allansmith and E. Senz ....p. 109

Observations on Acute Bronchiolitis in Infants.—Bacteriologic, serologic, and virologic studies on 73 infants acutely ill with bronchiolitis revealed that Hemophilus influenzae was isolated from nasopharyngeal cultures of 48 of the infants (typable strains from 35, non-typable from 13). Type-specific agglutinating antibodies developed during convalescence in 59. Diplococcus pneumoniae was cultured from 21. Complement-fixation tests on paired serum samples from 72 patients failed to show rising titres against the following viral antigens: Influenza A, B, C, and D; Adenovirus; CA; HA-1 and HA-2. One had rising titres to Influenza A. Nasopharyngeal washings from 46 infants failed to show cytopathological agents in monkey kidney or HeLa cell cultures.

Hemabsorption tests on 24 were all negative. This evidence supports earlier suggestions that H. influenzae may be an active etiological agent in acute bronchiolitis, and therapy should be directed toward its elimination.

Pneumonitis Induced by Experimental Infection.—In order to study further the relationship of Hemophilus influenzae to clinical acute bronchiolitis, experiments were undertaken to reproduce the characteristic pathological lesions by infecting newly born mice with bacteria recently isolated from infants with the disease. Classical bronchiolitis with interstitial pneumonia was demonstrated in microscopic sections of the lungs. The bacteria were recovered on culture. H. influenzae, types A, B, and E, produced identical pathological lesions. The addition of the bacteria-free filtrate of nasopharyngeal mucus from the original patients did not appear to influence the pattern of pneumonitis produced by H. influenzae alone. The filtrate alone did not produce detectable pathological lesions.

Aspirin and Salicylamide Suspension in Pediatrics.—In a clinical study of 206 infants and children hospitalized for various febrile conditions, it was found that salicylamide suspension had only minor antipyretic action. The effect of salicylamide was usually transient and poorly sustained, a small temperature drop of 1 to 1½ hours' duration being followed by a recurrence of fever. Aspirin, on the other hand, generally produced prompt and sustained antipyresis. A summary of the literature revealed no significant difference in acute toxicity of the 2 drugs toward laboratory animals. Since salicylamide is a poorer antipyretic than aspirin and offers no advantage in safety, there is no justification for substituting it for aspirin as an antipyretic.

Hirsutism in Adolescent Girls.—Two girls, 13, and 1 girl, 14, presented a rather unusual clinical picture characterized by hirsutism, obesity, mild enlargement of the clitoris, and menstrual irregularity. The urinary excretion of 17-ketosteroids, corticosteroids, and pregnanetriol was normal in each patient. Other studies failed to demonstrate evidence of altered adrenal cortical function. Abdominal exploration in each instance revealed the presence of polycystic ovaries characteristic of those described in patients with Stein-Leventhal syndrome.

Menghini Needle Biopsy of the Liver.—This report describes a new technique for needle biopsy of the liver in the pediatric age group. The Menghini R needle is used. Its singular advantage lies in the very short intrahepatic phase required (approximately 1 second). In addition, the authors employ manual compression of the chest cage to prevent sudden gasping. This combination has been successfully employed in 36 biopsies of the liver in 33 patients without any significant complication. Twelve of the patients were 2 years of age or less. The specimens obtained are of excellent quality. Only 2 failures were encountered. These were attributed to marked parenchymal *scarring, an uncommon finding in the* pediatric age group.

Diagnosis of Neonatal Jaundice.—This study was an extension of previous preliminary investigations which appeared to indicate that the technique of serial measurements of serum transaminase activity is a valuable diagnostic aid in neonatal jaundice. In the present investigation serial measurements of transaminase activity were obtained in an additional group of very young infants with jaundice due to pathological conditions, to delineate further the patterns of enzyme activity which appear to evolve for the varied causes of neonatal jaundice. These patterns of serum transaminase activity, as related to the clinical course, facilitate early and more accurate diagnosis in infants with this syndrome. Thereby, a twofold purpose may be served. Firstly, in correctible congenital malformations of the biliary tract early repair may be possible prior to the onset of appreciable cirrhosis. *Secondly, in medical types of neonatal jaundice* unnecessary and hazardous surgical interference may be discouraged.

Aerobic Bacterial Flora of the Throat of Children.—The effect of prolonged use of prophylactic doses of antibacterial agents was investigated in a convalescent home in which living accommodations were similar to a boarding school and not to a hospital. During the initial 4 months all patients received penicillin. Because of the frequency of strains of Hemophilus influenza and coagulase-positive staphylococci, 2 other protocols were serially employed. The 1st compared penicillin and tetracycline and the 2nd penicillin with no treatment. Group A streptococci and pneumococci were essentially absent. Throughout the investigation many penicillin-resistant and tetracycline-resistant staphylococci were isolated. Most were present prior to the study or upon admission. Few organisms were transferred between patients. Staphylococci isolated serially which were moderately resistant to penicillin became more resistant in 5 patients treated with it. Penicillin increased the frequency of Hemophilus influenza while tetracycline reduced it.

Studies in Sickle Cell Anemia.—There is no specific therapeutic agent for sickle cell anemia (SCA), but a well-planned program of management during periods of remission and of exacerbation of the disease can prolong life and make these patients more comfortable. During the asymptomatic phase of SCA, it is important to detect evidence of incipient infection and impending crises and to establish the individual homeostatic levels of certain hematological parameters. For clinical and therapeutic purposes, crises are often classified as "thrombotic" or "pain", "hemolytic", and "aplastic." Mild thrombotic crises may be successfully treated at the patient's home with anodynes, oral fluids, and bed rest. However, if the symptoms become refractory to these measures, hospitalization is advisable. Because of the intensity of symptoms and the frequent association of severe infection, children experiencing "hemolytic" or "aplastic" crises often require hospitalization in order to facilitate the administration of blood transfusions, oxygen, and other therapeutic agents. Blood transfusions are now used less frequently than formerly. However, children who exhibit shock, severe grades of anemia, and debilitating infections often show dramatic clinical improvement following judiciously administered blood. Splenectomy is not a curative procedure in this disease and should be performed only in carefully selected cases where evidence of hypersplenism can be clearly established. *The best results are achieved* when each patient is categorically appraised for individualized therapy which should be directed toward restoration of the child's own level of physiological homeostasis.

I. Irradiation of Mother While Shielding Embryonic Site.—Female rats were irradiated with from 400 r to 1400 r on the 9th day of gestation while the pregnant uterus was shielded from the irradiation. The 9th day was chosen to determine the importance of an indirect effect of irradiation on the fetus, because it was very sensitive to the teratogenic effect of irradiation. No congenital malformations were produced from irradiating only the mother. The fetal mortality did increase with higher doses of irradiation, and at 1400 r partial-body irradiation to the mother there was not only increased fetal loss but marked growth retardation. On the other hand, 400 r to the mother did not interfere with fetal growth. Thus, it appears that the teratogenic effect of irradiation is due to its direct effect on the fetus.

II. Irradiation of the Placenta.—A method of irradiating rat placental tissue while shielding the mother and embryo is described. Placentae were irradiated with 400 r on the 12th gestational day and the fetuses were examined for congenital malformations, growth retardation and fetal death. Controls consisted of fetus in the same litter which received no irradiation or 400 r while the placenta was shielded. Four hundred roentgens to the placenta did not interfere with fetal growth or increase fetal mortality. Furthermore, malformations were not produced. It appears that irradiation of the placenta on the 12th day with 400 r produces insignificant changes in the fetus. On the other hand, no broad generalizations can be assumed concerning the placenta's responsibility in the overall picture of congenital malformations.

Chondrodystrophia Congenita Punctata.—Fifty-four cases of chondrodystrophia congenita punctata from the world literature have been reviewed. The previously unreported case of an infant suffering from this disease with cataracts, who survived beyond the age of 2 years, is added. Observations reported in the literature were: Of 49 cases 21 were males; of 32, 12 were prematures by weight; of 32, 25 had contractures; of 30, 27 had proximal limb shortening; of 37, 26 were dwarfed; of 20, 13 had abnormal skin; of 13, 7 were mentally retarded; of 55, 17 had cataracts; of 48, 5 had multiple incidence. Deaths in first year of life numbered 17 (average age, 5 months). The presence of cataracts indicated a poor prognosis for life. Because of the familial incidence, the disease was thought to be hereditary.

Acta medica scandinavica, Stockholm

166:241-326 (no. 4) 1960. Partial Index

Hypogammaglobulinemia in Myeloma
R. D. Eastham and W. B. Yoeman............p. 241
Effect of Prednisone on B_{12} Absorption in Pernicious Anemia
H. P. Kristensen and T. Friis............p. 249
Post-Myocardial-Infarction Syndrome
O. J. Broch and J. Ofstad............p. 281

Post-Myocardial-Infarction Syndrome.—The authors report on 7 cases of a febrile complication following acute myocardial necrosis. The syndrome is characterized by pericarditis, pleurisy, and pneumonia, together with an increase in the erythrocyte sedimentation rate and a rise in temperature. Five of the cases reported were identified in a retrospective study of 500 patients treated for cardiac infarction between 1956 and 1958. Two other patients were treated later. The 7 patients were men aged from 41 to 81 years. Pericardial friction rub was heard in 4 patients during a period that varied between 2 days and 8 weeks after an antero-septal infarction. Pneumonia was present in 1 patient, pleurisy in 2, and rheumatic pain in 2. All had fever and an increase in the erythrocyte sedimentation rate. Therapy consisted in the administration of anticoagulants and was well tolerated by the 7 patients reported on. The authors call attention to the danger of complications and the need for administering anticoagulants with greatest care. The prognosis in the post-myocardial-infarction syndrome is good. The differential diagnoses that should be considered are a new infarction, pulmonary emboli, and pulmonary infection.

American Journal of Gastroenterology, New York

33:391-514 (April) 1960. Partial Index

Gastrointestinal Bleeding in Hemorrhagic Telangiectasia
J. A. Ecker, W. A. Doane, and others............p. 411
The Corticosteroid-Induced Peptic Ulcer
E. L. Dubois, J. G. Bulgrin, and G. Jacobson............p. 435
Experiences with Hemagglutination in Viral Hepatitis
L. M. Morrison, R. E. Hoyt, and others............p. 461
Lymphatic Varicosities of the Gastrohepatic Ligament
J. T. Nix and D. L. Wendt............p. 478

Gastrointestinal Bleeding in Telangiectasia.—Two cases of unexplained gastrointestinal bleeding in which the primary condition was hereditary hemorrhagic telangiectasia are reported. An 84-year-old woman had a sudden episode of melena which precipitated myocardial infarction and congestive heart failure. After 10 episodes of rectal bleeding the patient underwent emergency laparotomy. The right colon contained a considerable amount of blood, and several 1 to 2 mm. serosal telangiectasias were found in the distal ileum. Bleeding telangiectasias were scattered through the ileocecal valve and the cecum. Proximal and distal proctoscopic examination, colotomy, right colectomy, and ileotransverse colostomy were performed, and the patient made an uneventful recovery. The 2nd patient, a 39-year-old woman, was subjected to laparotomy because of suspected abdominal aneurysm and pancreatic neoplasm. Subserosal telangiectasias were found throughout the small intestines. The patient made an excellent recovery. The diagnosis was hereditary hemorrhagic telangiectasia with prognosis of possible hemorrhagic symptoms in the future. These cases illustrate the need for a differential diagnosis in gastrointestinal bleeders with or without a family or hereditary history of hemorrhagic telangiectasia.

American Journal of Surgery, New York

99:393-608 (April) 1960. Partial Index

Hyperparathyroidism: Diagnosis and Management
O. Cope............p 394
Thymectomy for Myasthenia Gravis
M. M. Musselman and J. W. Porter............p. 404
Hyperinsulinism
W. H. ReMine, D. A. Scholz, and J. T. Priestley............p. 413
Ulcerogenic Tumors of the Pancreas
R. M. Zollinger and T. V. Craig............p. 424
Adrenalectomy for Cushing's Syndrome
H. Mannix Jr., R. Karl, and F. Glenn............p. 449
Transabdominal Adrenalectomy for Endocrine Disease
E. H. Ellison............p. 497
Adrenalectomy and Thyroidectomy for Ascites
I. D. Baronofsky and J. W. Canter............p. 512
Diagnosis and Treatment of Testicular Tumors
J. F. Patton, D. N. Seitzman, and R. A. Zone............p. 525
Hypophysectomy for Metastatic Mammary Cancer
O. H. Pearson and B. S. Ray............p. 544
Total Adrenalectomy in Cancer of Prostate
D. A. Macfarlane and others............p. 562

Ulcerogenic Tumors of the Pancreas.—In 1955 the senior author, on the basis of 2 case reports illustrating the association of non beta islet cell tumors with severe peptic ulcer diathesis, had suggested a syndrome consisting of: (1) excessive gastric secretion; (2) fulminating and often atypically located peptic ulceration; and (3) non-insulin-producing islet cell tumor of the pancreas. The authors reappraise this syndrome in the light of corroborating evidence and of objections that have been raised against it. They emphasize that patients exhibiting a severe peptic ulcer diathesis or intractable watery diarrhea with a high output of acid gastric juice should be suspected of harboring a nonbeta islet cell tumor of the pancreas. Primary jejunal ulceration and failure of otherwise adequate gastric operations to control the acid gastric factor are seen with such frequency in patients with these tumors as to be practically pathognomonic. Careful search along the pancreatic wall of the duodenum for aberrant nodules during operations for ulcer has been productive. The rarity of the ulcerogenic tumor should not deceive the clinician when treating the "failures" following his favorite gastric operation. Total gastrectomy, rather than total pancreatectomy, remains the treatment of choice, along with resection of the tumor and its metastases when possible. Functioning tumors of other endocrine glands will be found in about 20% of patients with ulcerogenic pancreatic tumors, and these should be sought out and removed. The preservation of ulcerogenic tumors of the pancreas by deep freezing under sterile conditions is encouraged. Special studies of such material may eventually elucidate the etiology of the baffling problem of peptic ulcer.

Adrenalectomy for Cushing's Syndrome.—The authors review observations on 40 patients with adrenal cortical hyperfunction (Cushing's syndrome) who were treated at the New York Hospital, Cornell Medical Center during a period of 26 years. The ages of the patients ranged from 12 to 52 years at the time of diagnosis; there were 36 females and 4 males. The diagnosis was established either by surgical exploration or postmortem study. Two patients presented themselves prior to the era of steroid replacement and both died; one had a basophilic tumor, and the other an adrenal adenoma. In the era of steroid therapy, 38 patients received some form of surgical treatment, mostly total or bilateral subtotal adrenalectomy. Operations on the pituitary were carried out in 4 patients. One of these 4 patients had previously undergone subtotal adrenal extirpation. When she had a recurrence, her physician suggested hypophysectomy. The removed pituitary was histologically normal. The series included 31 patients with adrenocortical hyperplasia, 8 with adrenocortical adenoma and one with adrenocortical carcinoma. Bilateral total adrenalectomy in 1 stage seems to provide the best results. The management of induced Addison's disease has not been difficult. In addition to the 2 patients who died without surgery, 3 patients have died: 1 from metastatic cortical carcinoma, 1 from cerebral hemorrhage, and 1 from a brain abscess.

Hypophysectomy for Metastatic Mammary Cancer.—The authors review observations on 343 patients with metastatic mammary carcinoma who underwent surgical hypophysectomy. All except 9 of these patients had advancing metastatic disease; in the 9 patients the operation was carried out shortly after radical mastectomy, to test whether early, optimal endocrine therapy will provide more effective control than that carried out at a later stage of the disease. The operative procedure consisted of a coronal scalp incision, removal of the right frontal bone plate, division of the hypophyseal stalk, removal of the pituitary gland by curettage, abrasive swabbing and suction, and finally, exposure of the sella turcica to Zenker's solution. Maintenance therapy consisted of 37.5 mg. of cortisone and 120 mg. of desiccated thyroid orally per day. Some patients required posterior pituitary powder by nasal insufflation for control of thirst and polyuria. During periods of stress the patient usually required increased cortisone replacement. The patient who has undergone hypophysectomy has a normal appearance, normal mental and physical functions, and can lead a normal life. Of 144 patients who obtained remissions, 123 experienced regression and 21 arrest of their carcinomatous lesions. The mean duration of hypophysectomy-induced remissions was 12.3 months. The most reliable index for predicting a favorable response to hypophysectomy is a previous favorable response to oophorectomy in the premenopausal patient. Other factors, such as response to hormone therapy, duration of the cancer, age of the patient, and location and extent of metastases have some influence on the incidence of remissions, but are not particularly helpful in deciding on the mode of therapy for the individual patient. Hypophysectomy is recommended as initial treatment in postmenopausal patients and in those who have had previous favorable response from oophorectomy, provided adequate facilities are available to perform hypophysectomy.

Archives of Disease in Childhood, London

35:1-114 (Feb.) 1960. Partial Index

Abdominal Tumors in Infants and Children
C. E. Koop........p. 1
Primary Tumors of Liver in Infants and Children
H. W. Clatworthy Jr., E. T. Boles, and W. A. Newton........p. 22
New Operation for Treatment of Hirschsprung's Disease
B. Duhamel........p. 38
Incubator for Infants Undergoing Surgery
P. P. Rickman and J. M. Jenkins........p. 71
Surgical Aspects of Patent Ductus Arteriosus
J. J. Bickford........p. 92

Surgical Aspects of Patent Ductus Arteriosus.—Two series of patients with patent ductus arteriosus treated surgically are reported. The only method of closure used in the 1st series (108 children) was double ligature. There were 16 (14%) failures, all among patients with a ductus of 8 mm. diameter and over. In the 2nd series (120 children) simple ligature was used 70 times, with 5 (4%) recanalizations; ligature and transfixion suture were performed on 40 patients, and division on 10, with no recanalizations. Simple ligation is a safe and easy method of obliteration when the ductus diameter is 7 mm. or less. It may be even safer when combined with a transfixion suture. In ductus above 8 mm. in diameter division should be the method of choice. The 2nd series reported covers a period of transition in surgical policy; the failure rate of 4% is an improvement over the failure of 14% of the 1st series. Further reduction of the failure rate is probably dependent on more extensive use of division of the medium-sized ductus.

Arch. Instituto de cardiología México, México, D. F.

30:1-116 (Jan.-Feb.) 1960. Partial Index

Cardiac Lesions in Malaria Vivax
J. M. Herrera........p. 26
Causes of Death in Essential Arterial Hypertension
S. Zajarias, L. Méndez, and J. Ramos........p. 51
Thrombelastography in Diagnosis of Thrombophlebitis
J. Escudero and I. S. Wright........p. 76

Thrombelastography in Thrombophlebitis.—Fifteen patients with thrombophlebitis and 15 normal persons were examined by thrombelastography, a procedure which registers the variations in elasticity of the thrombus during the coagulation process. The blood sample is put into a steel cylinder which goes through a pendulum-like motion. A steel piston dips into the blood and as soon as coagulation starts piston and cylinder move together. The speed of this movement increases with the progressive formation of on the fetus, because it was very sensitive to the teratogenic effect of irradiation. No congenital malformations were produced from irradiating only the mother. The fetal mortality did increase with higher doses of irradiation, and at 1400 r partial-body irradiation to the mother there was not only increased fetal loss but *marked growth* retardation. On the other hand, 400 r to the mother did not interfere with fetal growth. Thus, it appears that the teratogenic effect of irradiation is due to its direct effect on the fetus.

II. Irradiation of the Placenta.—A method of irradiating rat placental tissue while shielding the mother and embryo is described. Placentae were irradiated with 400 r on the 12th gestational day and the fetuses were examined for congenital malformations, growth retardation and fetal death. Controls consisted of fetus in the same litter which received no irradiation or 400 r while the placenta was shielded. Four hundred roentgens to the placenta did not interfere with fetal growth or increase fetal mortality. Furthermore, malformations were not produced. It appears that irradiation of the placenta on the 12th day with 400 r produces insignificant changes in the fetus. On the other hand, no broad generalizations can be assumed concerning the placenta's responsibility in the overall picture of congenital malformations.

Chondrodystrophia Congenita Punctata.—Fifty-four cases of chondrodystrophia congenita punctata from the world literature have been reviewed. The previously unreported case of an infant suffering from this disease with cataracts, who survived beyond the age of 2 years, is added. Observations reported in the literature were: Of 49 cases 21 were males; of 32, 12 were prematures by weight; of 32, 25 had contractures; of 30, 27 had proximal limb shortening; of 37, 26 were dwarfed; of 20, 13 had abnormal skin; of 13, 7 were mentally retarded; of 55, 17 had cataracts; of 48, 5 had multiple incidence. Deaths in first year of life numbered 17 (average age, 5 months). The presence of cataracts indicated a poor prognosis for life. Because of the familial incidence, the disease was thought to be hereditary.

Acta medica scandinavica, Stockholm

166:241-326 (no. 4) 1960. Partial Index

Hypogammaglobulinemia in Myeloma
R. D. Eastham and W. B. Yoeman.........p. 241
Effect of Prednisone on B[illegible]
H. P. Kristensen and T. [illegible] 249
Post-Myocardial-Infarction Syndrome
O. J. Broch and J. Ofstad.........p. 281

Post-Myocardial-Infarction Syndrome.—The authors report on 7 cases of a febrile complication following acute myocardial necrosis. The syndrome is characterized by pericarditis, pleurisy, and pneumonia, together with an increase in the erythrocyte sedimentation rate and a rise in temperature. Five of the cases reported were identified in a retrospective study of 500 patients treated for cardiac infarction between 1956 and 1958. Two other patients were treated later. The 7 patients were men aged from 41 to 81 years. Pericardial friction rub was heard in 4 patients during a period that varied between 2 days and 8 weeks after an antero-septal infarction. Pneumonia was present in 1 patient, pleurisy in 2, and rheumatic pain in 2. All had fever and an increase in the erythrocyte sedimentation rate. Therapy consisted in the administration of anticoagulants and was well tolerated by the 7 patients reported on. The authors call attention to the danger of complications and the need for administering anticoagulants with greatest care. The prognosis in the post-myocardial-infarction syndrome is good. The differential diagnoses that should be considered are a new infarction, pulmonary emboli, and pulmonary infection.

American Journal of Gastroenterology, New York

33:391-514 (April) 1960. Partial Index

Gastrointestinal Bleeding in Hemorrhagic Telangiectasia
J. A. Ecker, W. A. Doane, and others.........p. 411
The Corticosteroid-Induced Peptic Ulcer
E. L. Dubois, J. G. Bulgrin, and G. Jacobson.........p. 435
Experiences with Hemagglutination in Viral Hepatitis
L. M. Morrison, R. E. Hoyt, and others.........p. 461
Lymphatic Varicosities of the Gastrohepatic Ligament
J. T. Nix and D. L. Wendt.........p. 478

Gastrointestinal Bleeding in Telangiectasia.—Two cases of unexplained gastrointestinal bleeding in which the primary condition was hereditary hemorrhagic telangiectasia are reported. An 84-year-old woman had a sudden episode of melena which precipitated myocardial infarction and congestive heart failure. After 10 episodes of rectal bleeding the patient underwent emergency laparotomy. The right colon contained a considerable amount of blood, and several 1 to 2 mm. serosal telangiectasias were found in the distal ileum. Bleeding telangiectasias were scattered through the ileocecal valve and the cecum. Proximal and distal proctoscopic examination, colotomy, right colectomy, and ileotransverse colostomy were performed, and the patient made an uneventful recovery. The 2nd patient, a 39-year-old woman, was subjected to laparotomy because of suspected abdominal aneurysm and pancreatic neoplasm. Subserosal telangiectasias were found throughout the small intestines. The patient made an excellent recovery. The diagnosis was hereditary hemorrhagic telangiectasia with prognosis of possible hemorrhagic symptoms in the future. These cases illustrate the need for a differential diagnosis in gastrointestinal bleeders with or without a family or hereditary history of hemorrhagic telangiectasia.

American Journal of Surgery, New York

99:393-608 (April) 1960. Partial Index

Hyperparathyroidism: Diagnosis and Management
O. Cope.........p 394
Thymectomy for Myasthenia Gravis
M. M. Musselman and J. W. Porter.........p. 404
Hyperinsulinism
W. H. ReMine, D. A. Scholz, and J. T. Priestley.........p. 413
Ulcerogenic Tumors of the Pancreas
R. M. Zollinger and T. V. Craig.........p. 424
Adrenalectomy for Cushing's Syndrome
H. Mannix Jr., R. Karl, and F. Glenn.........p. 449
Transabdominal Adrenalectomy for Endocrine Disease
E. H. Ellison.........p. 497
Adrenalectomy and Thyroidectomy for Ascites
I. D. Baronofsky and J. W. Canter.........p. 512
Diagnosis and Treatment of Testicular Tumors
J. F. Patton, D. N. Seitzman, and R. A. Zone.........p. 525
Hypophysectomy for Metastatic Mammary Cancer
O. H. Pearson and B. S. Ray.........p. 544
Total Adrenalectomy in Cancer of Prostate
D. A. Macfarlane and others.........p. 562

Ulcerogenic Tumors of the Pancreas.—In 1955 the senior author, on the basis of 2 case reports illustrating the association of non beta islet cell tumors with severe peptic ulcer diathesis, had suggested a syndrome consisting of: (1) excessive gastric secretion; (2) fulminating and often atypically located peptic ulceration; and (3) non-insulin-producing islet cell tumor of the pancreas. The authors reappraise this syndrome in the light of corroborating evidence and of objections that have been raised against it. They emphasize that patients exhibiting a severe peptic

fibrin and solidification of the clot, then decreases as the thrombus becomes flaccid, until fibrinolysis is completed. The principal components of the thrombelastogram (TE) as registered by a kymograph are: reaction time (r), coagulation time (k), and maximal amplitude (ma) of the tracing. The TE's in this series showed that in normal persons r varied between 8.2 and 19 minutes, k between 3 and 8.5 minutes, and ma, between 45 and 69 mm. Characteristic changes in patients with either recent or old thrombophlebitis were shortening of r and k, and increase of ma. Eighty per cent of the patients had a ma of 64 mm. or more, while 73% had an r shorter than 9.5 minutes. Thrombelastography, therefore, is a useful, although not specific, method of diagnosis in recent or old thrombophlebitis.

British Medical Journal, London

1:985-1070 (April 2) 1960. Partial Index

Clinical Sense
R. Asher .... p. 985
Infection of Burns
E. J. L. Lowbury .... p. 994
Acute Ischaemia in Limb Injuries
E. G. Hardy and D. J. Tibbs .... p. 1001
Chronic Arm Oedema After Treatment for Breast Cancer
A. H. W. Nias .... p. 1005
"Premature" Children at Primary Schools
J. W. B. Douglas .... p. 1008
Sarcomatous Change in Brothers with Diaphysial Aclasis
J. D. S. Knight .... p. 1013

Infection of Burns.—The author's observations on patients with burns admitted to the Birmingham Accident Hospital, England, showed that bacteria growing in deep burns can cause both local and general damage. Streptococcus pyogenes which has been reduced to negligible importance in other fields of surgery, is still the most formidable of the local pathogenic agents in burns. It causes skin-graft failure, delayed healing, and deformity if it is not removed from the burn. Pseudomonas aeruginosa, Staphylococcus pyogenes var. aureus, Proteus, and other bacteria can also cause local damage, and are today more important as the cause of septicemia and fatal infection than Str. pyogenes. It has proved possible to keep some of the burns free from Str. pyogenes, Staph. pyogenes var. aureus, Pseudomonas aeruginosa, and some of the coliform bacilli by a combination of physical and local chemotherapeutic barriers. The combined application of polymyxin, chlorhexidine, i. e., 1,6-di-(4′-chlorophenyldiguanido) hexane, and neomycin has been found effective in prophylaxis. Though the protection thus afforded is imperfect, it has proved clinically valuable. There is a dilemma involved in the choice between encouraging the formation of a dry adherent crust and applying chemoprophylactic creams which keep the burn moist; when the former method is used, pathogenic agents appear more frequently but perhaps cause less damage than they do when they can multiply not only in the burn but also in wet dressings. Future studies will include an attempt to combine the advantages of a relatively dry surface and of chemoprophylactic cover.

Sarcomatous Change in Brothers with Diaphysial Aclasis.—The author reports on a family in which 7 male and 6 female members had diaphysial aclasis (multiple cartilaginous exostoses). Three of the affected male members, who were brothers, had sarcomatous change as a rare but well recognized complication of diaphysial aclasis. The 1st of the 3 died of chondrosarcoma of the ilium at the age of 54 years, the 2nd died of a sarcoma of the "shin," at the age of 22, and the 3rd died of a sarcoma of his pelvic bone at the age of 24. Chondrosarcomatous change should be suspected in any exostosis that shows renewed growth at any time after the age of 20 years. In many cases it is difficult to confirm the diagnosis without biopsy. Biopsy was available only in the 1st of the 3 brothers and confirmed the clinical diagnosis of chrondrosarcoma. Twenty-six other cases of chondrosarcoma complicating diaphysial aclasis were collected from the literature. In none of these families did more than 1 member show this complication.

Indiana State Medical Assn. Journal, Indianapolis

53:613-802 (April) 1960. Partial Index

Malignant Bone Tumors of Childhood
G. J. Garceau .... p. 645
Neoplasms of Reticuloendothelial System in Children
R. J. Rohn, W. H. Bond, and others .... p. 649
Genito-Urinary Malignancies in Children
D. H. Yurdin .... p. 671
Thyroid Cancer in Childhood and Adolescence
R. K. Gibson .... p. 676
Seven Primary Malignancies: Multiple Malignancies
E. W. Graham and E. B. Smith .... p. 683

Seven Primary Malignancies: Multiple Malignancies.—A review of 9,145 autopsy records at the Indiana University Medical Center, Indianapolis, from 1914 to 1959, revealed 1,501 patients (16.4%) who had cancer. Thirty of the 1,501 patients (2%) had 2 or more primary malignant neoplasms. The authors discuss the criteria of and review the literature on multiple primary malignancies. In further analyzing the data on the 30 cases, they present the case history and review the autopsy findings in a 79-year-old man who had 7 primary malignant neoplasms involving 5 different organ systems: an epidermoid carcinoma of the cheek, an epidermoid carcinoma of the nose, chronic lymphocytic leukemia, an epidermoid carcinoma of the bronchus, adenocarcinoma of the prostate, adenocarcinoma of the ascending colon, and locally invasive adenocarcinoma of a polyp in the descending colon. Lymphoma or leukemia coexistent with a second primary malignant neoplasm was present in 8 cases. The 30 patients with multiple primary malignancies included 16 men and 14 women. The average age of women with multiple primary malignancies was 57.2 years. The average age of men with multiple malignancies was 70.9 years. The fact that women have multiple primary malignant neoplasms at an earlier age than men is probably related to the susceptibility of the female sex organs to carcinoma. Of the 14 women with multiple malignant tumors, 9 had malignant tumors of the cervix and breast, 5 of the cervix of the uterus, and 4 of the breast.

Journal Clin. Endocrinol., Springfield, Ill.

20:495-664 (April) 1960. Partial Index

Estrogens and Adrenocortical Function in Man
R. E. Peterson, G. Nokes, and others .... p. 495
Steroid Excretion in Hypophysectomized Women, and Corticotropin
H. Wilson, M. B. Lipsett, and L. C. Butler .... p. 534
Metabolic Effects of Triiodothyronine and Thyrotropic Hormone
B. S. Hetzel, J. S. Charnock, and B. F. Good .... p. 556
Occurrence and Treatment of Hypothyroidism Among Alcoholics
M. Goldberg .... p. 609
Coexistence of Pheochromocytoma and Adrenocortical Hyperplasia
G. A. Williams, C. L. Crockett, and others .... p. 622
Cushing's Syndrome with Multinodular Adrenal Glands
H. D. Mosier, P. J. Flynn, and others .... p. 632

Hypothyroidism Among Alcoholics.—While investigating symptoms of early hypothyroidism the author found among the first several patients who had both clinical and laboratory evidence of thyroid deficiency, 2 who admitted a rapidly progressing inability to limit their alcohol intake. Within a few months following the correction of hypothyroidism by replacement therapy, both of these patients remarked that they found it easier to control their drinking. This response, together with observations by Richter in animals, prompted the investigation of the thyroid status of 33 alcoholics (30 men and 3 women) ranging in age from 26 to 48 years. Thyroid function was estimated clinically and the laboratory tests included the determination of (1) the serum protein-bound iodine (PBI) concentration before and 24 hours after the injection of 10 international units of thyroid-stimulating hormone (TSH), (2) basal metabolic rate (BMR), (3) serum cholesterol concentration, and (4) the electrometric recording of the Achilles tendon *reflex* time. Twenty-one of the 33 alcoholic patients were found to be thyroiddeficient. When treated with desiccated thyroid (180 mg. daily on the average) or L-triiodothyronine (100 mcg. daily, average), impressive results were obtained both in regard to improvement of hypometabolic symptoms and drinking patterns. Fifteen patients had an excellent response, 8 a good response, and 10 a fair or poor response. As judged by curtailment of drinking, hypothyroid patients responded better than did euthyroid patients; sudden discontinuation of medication exacerbated the symptoms of alcoholism in several patients.

J. Thoracic & Cardiovas. Surgery, St. Louis

39:417-554 (April) 1960. Partial Index

Stationary Vertical-Screen Oxygenator (Mayo-Gibbon)
M. B. Levin and others ....p. 417
Rotating-Disc Blood Oxygenator of Improved Efficiency
J. J. Osborn and others .... p. 427
A Modification of the Clowes Membrane Lung
E. Converse Peirce II ....p. 438
Anaphylactoid Shock Due to Homologous Blood Exchange
J. W. Dow and others ....p. 449
Veno-Arterial Pumping in Dogs
H. H. Patt ....p. 464
Potassium Ion as a Cardioplegic Agent
A. Kaplan and B. Fisher ....p. 468
Duodenobronchial Fistula
J. L. Keeley and T. A. Campbell ....p. 538

Duodenobronchial Fistula.—The authors report the occurrence of a duodenobronchial fistula in a 67-year-old man who was admitted to hospital because of a productive cough, weakness and weight loss of 8 weeks duration. A diagnosis of bronchiectasis of the right lower lobe had been made before the patient's admission to hospital. A chest roentgenogram revealed diffuse mottling of the base of the right lung, some shift of the mediastinum to the right, and elevation of the diaphragm on the right. These findings were considered compatible with the clinical diagnosis of bronchiectasis. Roentgenograms of the intestinal tract showed that barium left the duodenal lumen and reached the bronchial radicles of the lower lobe of the right lung through a fistulous communication. Attempts to pass a long tube beyond the fistulous tract and the distorted duodenum for feeding purposes and to decrease the contamination of the tracheobronchial tree were unsuccessful. It was thought that closure of the fistula would decrease the productive cough; at operation the duodenum was found to be separated from the fistulous tract, and the opening in the duodenum was closed. The gall bladder, which contained 2 stones and did not appear to be involved in the fistula formation, was removed as an incidental procedure. The productive cough stopped after the operation, and x-ray studies showed clearing of the haziness in the right lower lobe. From the findings in this patient, a perforated duodenal ulcer appears to be the most likely original lesion. No report of a similar fistulous communication was found in the literature, but a variety of pathological conditions below the diaphragm, which eventually communicated with the bronchial tree, were noted. A summary of these widely scattered reports has been presented.

Potassium Ion as a Cardioplegic Agent.—The authors studied the metabolism of the potassium ion during cardioplegia in 32 dogs, 16 of which were subjected to total cardiac bypass, at the onset of which cardioplegia was produced by the injection of a solution of potassium citrate, isotonic sodium chloride solution, and heparin containing radioactive potassium. The other 16 dogs were subjected to hypothermia with coronary perfusion, and cardiac arrest was produced by the injection of an identical potassium solution. Previous studies by the authors in normothermic and hypothermic animals had shown that reversibility of cardioplegia was not uniformly related to the amount of potassium injected or to its myocardial concentration, and that "washing out" potassium did not imply a resumption of normal rhythm. The results of the experiments performed in the 32 dogs confirmed the previous findings. They also supplied evidence that once potassium-induced cardioplegia was accomplished, its reversibilty was largely beyond the author's control. Mechanical means are effective only in "washing out" the potassium accumulated in the vascular space. Re-establishment of normal intracellular and extracellular equilibrium of this ion may be dependent on other factors. There is an uneven distribution of radioactive potassium within the heart; the greatest amount was found in the middle third of the ventricular septum, which may explain the frequent and persistent arrhythmias which occur after the employment of this agent. Experimental data suggest that the indiscriminate use of potassium as a cardioplegic agent is hazardous.

Zeitschrift f. d. ges. innere Medizin, Leipzig

15:235-282 (March 1) 1960. Partial Index

Pernicious Anemia and Diabetes Mellitus
G. Panzram..................p. 239
Impairment of Liver in Infectious Mononucleosis
K. Kouba and K. Mašek..................p. 244
Kalium Content of Damaged Cardiac Muscle
U. Mey..................p. 255
Myocarditis in Adults with Coxsackie B_3 Virus Disease
J. Müller and V. Kašová..................p. 260

Pernicious Anemia and Diabetes Mellitus.—Of 1,059 patients with diabetes mellitus and 117 patients with pernicious anemia seen by the author at the clinic of the Medical Academy, Erfurt, Germany, between 1951 and 1959, 10 had diabetes mellitus and simultaneous pernicious anemia. Of 7,129 patients with diabetes mellitus and 385 patients with pernicious anemia who attended various centers, including the medical clinic in Erfurt, 21 had diabetes mellitus and simultaneous pernicious anemia. Of the 117 patients with pernicious anemia seen at the medical clinic in Erfurt, 10 (8.5%) had diabetes mellitus. This incidence of diabetes mellitus among patients with pernicious anemia is much higher than the incidence of diabetes mellitus to be expected today, and the incidence has increased as compared with previous statistics. Of the 7,129 patients with diabetes mellitus, 16 (0.22%) had pernicious anemia; this incidence of pernicious anemia is not higher than might have been expected in the general population. Among the 117 patients with pernicious anemia and diabetes mellitus, the onset of pernicious anemia more frequently preceded that of diabetes mellitus. In nearly 50% of all the patients with both the diseases reported on, the onset of pernicious anemia preceded that of diabetes mellitus. This finding deserves particular consideration, since diabetes mellitus usually becomes manifest at an earlier age than pernicious anemia. Impairment of the utilization of glucose due to vitamin B_{12} deficiency, which has been demonstrated clinically and experimentally in cases of pernicious anemia, justifies the assumption that in patients with pernicious anemia and simultaneous diabetes mellitus there may be a pathogenic relationship between the two diseases.

Tennessee State Medical Assn. Journal, Nashville

53:129-174 (April) 1960. Partial Index

Gastrointestinal Bleeding Due to Meckel's Diverticulum
R. W. Newman and F. S. Jones .... p. 129
Complications of Pelvic Perfusion with Nitrogen Mustard
D. M. Sholes Jr. and H. H. Jenkins .... p. 134
Trimethobenzamide and Pyridoxine in Vomiting of Pregnancy
O. L. Davidson .... p. 140

Gastrointestinal Bleeding Due to Meckel's Diverticulum.—Of 29,941 children admitted to the pediatric wards of 4 general hospitals between 1948 and 1958, 15 had significant hemorrhage into the gastrointestinal tract. Meckel's diverticulum with ulceration was the cause of the bleeding in 5 of the 15 patients. Of these 5 children, 4 were aged from 9 to 18 months, and 1 was 14 years old. The bleeding was massive in character and rectal in location. None of the 5 children had bloody vomitus. The patients showed signs of blood loss by pallor, sweating, rapid pulse and lethargy or collapse. The hematocrit values were 30% or less. Bleeding and clotting times were normal. Gastrointestinal roentgenograms were obtained from 3 patients and the findings were normal in all of them. All patients were operated on and resection of Meckel's diverticulum and the ulcerated area of the adjacent ileum was carried out. All the patients recovered and did not have further bleeding. Massive rectal bleeding is the most common complication of a Meckel's diverticulum in children. In any patient in the pediatric age group with gross melena of painless character with shock-like symptoms, the diagnosis of a bleeding Meckel's diverticulum should be suspected. The pathological changes leading to ulceration and hemorrhage in Meckel's diverticulum are related to the presence of gastric mucosa in the pouch. This gastric mucosa is of the fundal type containing acid-secreting parietal cells. The acid is capable of causing peptic erosion of the unprotected adjacent ileal mucosa. Treatment consists of emergency blood replacement and surgical removal of the Meckel's diverticulum and the ulcerated area of the adjacent ileum.

Semana Médica, Buenos Aires

116:139-170 (Feb. 11) 1960. Partial Index

Peripheral Blood and Bone Marrow in Venous Cirrhosis
M. Meeroff and others .... p. 139
Prosthesis in Longitudinal Talipes Planovalgus
M. Schnir .... p. 148
Secondary Reactions to Heterologous Serum
M. Suli .... p. 159

Peripheral Blood and Bone Marrow in Cirrhosis.—The changes occurring in the peripheral blood and bone marrow of patients with venous cirrhosis were studied in 28 subjects. The peripheral blood count showed anemia in 18 patients, although in only 9 (32.14%) was the blood red cell count below 3,500,000. Macrocytosis, usually with hyperchromia, was observed in 53.57% of the patients (13 anemic and 2 nonanemic). Plasmocytic reactions in the marrow were found in 25 patients (89.25%), and leukocytosis in 7 (25%). Two sets of factors present in venous cirrhosis are suggested to explain the pathogenesis of the blood and bone marrow changes: (1) Macrocytosis and bone marrow plasmocytic reactions are related to constitutional factors and gastrointestinal conditions such as intestinal malabsorption, insufficient nutrition, and the hepatic lesion itself, all of which causes changes in the utilization of cyanocobalamine and folic acid. (2) Leukocytosis, which indicates the seriousness of the hepatic process, may be related to the presence of secondary infection.

Pediatrics, Springfield, Ill.

25:531-560 (March, pt. 2) 1960

Congenital Coronary Arteriovenous Fistula
B. M. Gasul and others .... p. 531

Congenital Coronary Arteriovenous Fistula.—An abnormal communication of the coronary arterial tree with a cardiac chamber can now be diagnosed during life and can be operated on without the use of hypothermia or extracorporeal circulation. This fistula usually communicates with the right atrium, the right ventricle, or the main pulmonary artery, forming an arteriovenous fistula; or, very rarely, it may communicate with the left atrium or left ventricle, forming an internal fistula within the systemic circulation. The authors tabulate data on 52 patients with this form of anomaly which they collected from the literature, and they present detailed histories of 5 patients. The 5 patients ranged in age from 19 years down to 3 weeks. Practically all of them were admitted for the investigation of heart murmurs. The primary diagnosis in the first 3 patients was patent ductus arteriosus. This diagnosis was changed in the 3rd patient, on the basis of angiocardiographic studies before operation, to ruptured aortic sinus of Valsalva. This same diagnosis was made in the 4th patient, since the angiocardiographic features in this patient resembled those in the 3rd patient. The 5th patient, the 3-week-old infant, was the only 1 of the 5 in whom the coronary arteriovenous fistula was accompanied by patent ductus arteriosus. Corrective surgery is planned for this child when it is somewhat older. In the other patients surgical treatment has proved successful.

Minerva chirurgica, Turin

15:243-290 (March 15) 1960. Partial Index

Bilateral Tumor of Carotid Body
A. Polito and G. Catucci .... p. 250
Carcinoma of Colon: Clinical-Statistical Study
E. Uberti .... p. 260
Trypsin in Cranial Trauma and Brain Surgery
M. Gazzaniga, C. Arisi, and E. Sabbadini .... p. 271

Trypsin in Cranial Trauma and Brain Surgery.—Twenty patients with cranial trauma and 20 who had undergone different types of brain surgery were studied. Ten patients in each group were treated with trypsin; the others served as controls. The cerebrospinal fluid pressure, increased in both the traumatized patients and those who underwent neurosurgery, reached a highest point on the second posttraumatic or postoperative day; it decreased slowly in the "no-trypsin" patients, returning to practically normal values on the 15th day. In the trypsin-treated patients the cerebrospinal fluid pressure fell from the first 2 days of therapy and reached normal values within the 4th and 6th days. All the neurological symptoms subsided simultaneously, with return of the vegetative functions to normal and an earlier recovery of consciousness. Trypsin develops an antiedematous effect, probably secondary to its anti-inflammatory properties, acting as a real local diuretic. Its use in cranial trauma and in neurosurgery is advantageous in the prevention and cure of 1 of the most dangerous complications, cerebral edema.

Tidsskrift for den norske laegeforening, Oslo

80:299-336 (March. 15) 1960. Partial Index

Hypertrophic Pulmonary Osteoarthropathy
299
T. Gundersen and F. Marstrander ....p. 301
Strangulation Ileus with Unusual Symptomatology
O. Bernstein ....p. 305

Hypertrophic Pulmonary Osteoarthropathy.—Hypertrophic pulmonary osteoarthropathy is usually secondary to diseases of the respiratory tract. The possibility of bronchial cancer as the cause should be considered. The syndrome of hypertrophic pulmonary osteoarthropathy is marked by clubbed fingers, arthritic-rheumatoid pain, enlargement of hands and feet, and periostitis. Clubbing may be the 1st symptom of malignant pulmonary disease and may appear long before symptoms from the respiratory tract appear. In 17 of 22 patients the interval between the occurrence of joint symptoms and the diagnosis of lung disease varied from 1 to 57 months. The symptoms 1st noticed by the patients are usually arthralgia and rheumatoid pain. The pain and other symptoms recede after resection of the lung tumor. The pathogenesis of the disease is unknown. The nature of the tumor does not seem to play a part in the origin of the osteoarthropathy, but the syndrome is most often connected with tumors situated peripherally in the lungs. The commonly mistaken diagnosis is rheumatism. In a man aged 46, a skin tumor on the back was excised in 1954 and a local recurrence was removed one year later. Two years later arthritic-rheumatoid pain set in, with periostitis and clubbing. Roentgen examination revealed pulmonary tumor and the lower lobe of the right lung was removed. After the operation the symptoms disappeared, but the general condition deteriorated and the patient died 2 months later. The diagnosis was metastasis from malignant tumor.

Radiology, Syracuse, N. Y.

74:177-352 (Feb.) 1960. Partial Index

Logical Analysis in Roentgen Diagnosis
L. B. Lusted....p. 178
Chronic Bronchitis and Emphysema at Bronchography
A. K. Freimanis and W. Molnar....p. 194
Orbital Hypotelorism, Arhinencephaly, Trigonocephaly
C. Currarino and F. N. Silverman....p. 206
Congenital Mesodermal Dysmorpho-Dystrophy
S. B. Feinberg....p. 218
Mandibulofacial Dysostosis
J. J. Stovin and others....p. 225
Silo-Filler's Disease
E. A. Cornelius and E. H. Betlach....p. 232

Silo-Filler's Disease.—The authors review 12 cases of silo-filler's disease, from the literature and describe 2 cases, one of which was subacute bronchopneumonia with bronchiolitis fibrosa obliterans, and the other was acute chemical bronchopneumonia. The patients had been exposed to nitrous fumes arising from a silo filled with fresh corn silage. Almost all patients noted the immediately irritative effect of the gas. Two clinical groups of patients could be distinguished: those in whom severe illness developed immediately after exposure; and those in whom early morbidity was followed by remission, which in turn was succeeded by relapse. Pulmonary fibrosis and obstructive emphysema are possible complications in delayed cases. Acurate evaluation requires pulmonary function tests and, possibly, lung biopsy. Oxygen and bed rest are indicated in all active cases with respiratory insufficiency. Antibiotics are of prophylactic value. Six of the total of 14 patients were treated with adrenal cortical hormone. It seemed to be of little value in those patients with pulmonary edema or acute pneumonia, but it has been of definite value in those in whom severe illness developed later. These patients recovered completely and soon returned to work; whereas, some of those with bronchiolitis obliterans, who did not receive steroids, were limited in their physical activity for many months.

Revista Chilena de Pediatria, Santiago

31:55-108 (Feb.) 1960. Partial Index

Causes of Death of Prematures in 1st Week of Life
G. Agüero and others....p. 55
Oxyuriasis in Children
F. Donoso and I. Colodro....p. 65
Fatal Case of Generalized Reaction to BCG Vaccination
A. Ariztia and others....p. 70

Fatal Reaction to BCG Vaccination.—A newborn girl received, on her 2nd day of life, an intradermal vaccination with BCG at the Instituto Bacteriológico de Chile. At 1 month of age she developed symptoms of whooping cough. At 3½ months the infant was hospitalized with a diagnosis of bronchopneumonia and dystrophy. Tuberculin reactions and laboratory test results were negative. The patient was treated with penicillin, chloramphenicol, and achromycin without any improvement. The suspicion that the refractory symptoms might be caused by an unforeseen reaction to the BCG vaccination led to treatment with isoniazid and streptomycin, but these also failed to bring about any improvement. The infant died at the age of 4½ months. Autopsy revealed lesions, at the site of the BCG inoculation, in the lymph nodes, lungs, and spleen. There was, in these organs, an inflammatory reaction with exudate of lymphocytes, histiocytes, and epithelioid cells resembling those found in tuberculous lesions, without the characteristic tubercles or caseation. Around and inside these lesions there was a number of acid-fast bacilli with characteristics of inoculation and culture similar to those of BCG. Inoculation with material obtained at autopsy produced in experimental animals only discrete lesions which healed quickly. Two possible explanations are suggested in this case: the generalized complication might be the result of an increase in virulence of the bacillus used for inoculation; it might have resulted from a special individual condition or from pre-existing lesions which created an appropriate ground for dissemination of the BCG.

Semana Médica, Buenos Aires

67:29-56 (Jan. 14) 1960. Partial Index

Articular Manifestations in Meningococcic Infections
J. M. A. Moreira and A. Tchoulamjan....p. 29
Olfactory Hallucination and Impending Thrombosis
J. P. Käfer and others....p. 44

Olfactory Hallucination and Impending Thrombosis.—A 57-year-old man experienced an unpleasant sensation of smelling ammonia. The sensation lasted for periods of one-half hour to 2 hours and recurred 4 to 6 times a day. Two weeks later the patient noticed a pulling of the labial commissures to the right. Four months later the patient was hospitalized because of progressive hemiparesis of the right side, predominantly faciobrachial, with pyramidal syndrome. An electroencephalogram revealed synchronous basal discharges. The possibility of a deep temporal tumor led to an arteriographic study of the right side which showed that the contrast medium stopped 2 mm. from the bifurcation of the common carotid artery, with visualization of only the external carotid system. A delayed roentgenogram also failed to show the internal carotid artery. These findings established the diagnosis of thrombosis of the right carotid artery. The olfactory hallucinations, which are not a part of the usual clinical picture in carotid thrombosis, are explained by the fact that since the blood supply to the area of the olfactory bulb and the tonsilar nucleus comes from the terminal branches of the internal carotid artery (the anterior cerebral and the sylvian), the total occlusion of the main carotid trunk is likely to produce olfactory disorders.

Southern Medical Journal, Birmingham, Ala.

53:257-384 (March) 1960. Partial Index

Fractures of the Femur in Children
J. C. Hughston....p. 299
Amphotericin B in Cryptococcosis of Central Nervous System
G. W. Smith and others....p. 305
Bleeding in Diverticular Disease of the Colon
F. J. Burns....p. 312
One Stage Colectomy, Proctectomy, and Ileostomy for Colitis
J. M. Donald and W. N. Viar....p. 335
The Problem of the Ruptured Intervertebral Disk
H. H. Karr....p. 341
Appendectomy Incidental to Cesarean Section
P. C. Schreier and J. D. Myers....p. 359
"Compensation" Neurosis
T. L. L. Soniat....p. 365

Amphotericin B in Cryptococcosis of Central Nervous System.—The authors present the histories of 4 patients with cryptococcosis of the central nervous system. Patients 1, 3, and 4 were initially thought to have a brain tumor or other intracranial mass lesion, and the 2nd patient was suspected of having tuberculous meningitis prior to definitive laboratory studies. The yeast-like fungus, *Cryptococcus neoformans* (Torula histolytica), is the most common cause of mycotic meningitis and meningo-encephalitis in man. Since the 1st case was diagnosed in 1914, nearly 300 cases have been reported. Cryptococcosis of the central nervous system usually manifests itself as a chronic or low grade subacute meningo-encephalitis. There may be localized or focal neurological signs which suggest an intracranial mass lesion. Obstruction of the flow of cerebrospinal fluid produces all the signs of increased intracranial pressure, including papilledema. The spinal fluid findings are often similar to those of tuberculous meningitis. The differentiation frequently rests upon identification of the yeast fungi in the India ink preparation or on culture. The organism appears as a round or oval single-budding, thick-walled, yeast-like cell, 5 to 10 μ in diameter and surrounded by a refractile gelatinous capsule which may be twice the diameter of the organism proper. The authors stress the importance of suspecting cryptococci when increased numbers of mononuclear cells are found in the spinal fluid. They found amphotericin B to be effective in the treatment of the 4 patients with cryptococcosis, but they feel that long-term follow-up will be required to determine the final result.

Ugeskrift for laeger, Copenhagen

122:271-310 (March 3) 1960. Partial Index

Schilling Test: Background and Importance
E. Bierring and I. Ebbesen....p. 277
Solitary Liver Abscess in the Newborn Infant
C. M. Madsen and N. Secouris....p. 281

Solitary Liver Abscess in the Newborn Infant.—In cases of peritonitis or sepsis in the newborn infant, attention should be directed to possible umbilical infection. Grave general infection can originate from the umbilicus, even when local signs of infection are slight or are absent. Liver abscesses in the newborn infant seem to occur in 2 forms which differ both as to course and morphology. The acute form is a link in a general sepsis, where multiple small abscesses are found postmortem in the liver. The infection often enters through the umbilicus. In a subacute form, with less violent course, 1 or more larger abscesses in the liver are found. The portal of entry for the bacteria appears always to be the umbilicus, and the infection reaches the liver via the umbilical vein. The protracted course in this form allows diagnosis to be made in life, and makes possible surgical treatment with prospect of recovery. The case reported of solitary abscess of the liver in a newborn infant is ascribed to umbilical infection. Apparently only 11 cases of localized liver abscess in infants, originating from umbilical infections, have been described.

Revista Médica de Chile, Santiago

88:1-78 (Jan.) 1960. Partial Index

Prognostic Factors in Cardiac Insufficiency
E. Medina, R. Florenzano and others....p. 5
Treatment of Chronic Myeloid Leukemia with Myleran
G. Ducach, J. Granic, and others....p. 36
Hormonal Treatment of Psoriasis in Women
J. Feferholtz and others....p. 42

Treatment of Chronic Myeloid Leukemia.—Thirty-five patients with chronic myeloid leukemia were treated with busulfan (Myleran) administered orally, 6 mg. daily, until the leukocyte count fell to 30,000 per cubic millimeter. The dose was then decreased to 4 mg., and later, to 2 mg. The total dose for each remission fluctuated between 78 and 448 mg. The symptoms abated in all patients except 1 in whom no clinical or hematological response was obtained. Signs of remission were increase in appetite, weight gain, and a general feeling of well-being. The spleen decreased in size; abdominal distension and dyspepsia diminished. The reduction in leukocyte count was noticeable in the 1st week of therapy; the initial leukocyte count (80,000 to 400,000 per cubic millimeter) fell to from 20,000 to 30,000 within 1 month. The duration of the remission varied from 1 month in 1 patient to 5 years in another. At the end of 5 years 17 patients were living, 7 had died, and 11 could not be contacted. Side-effects were renal colic in 5 patients, amenorrhea in 3, urticaria in 2, and medullary aplasia in 1. Busulfan is a choice palliative treatment in chronic leukemia, allowing the patients to resume habitual tasks during the remission periods.

Hormonal Treatment of Psoriasis in Women.—Two aspects in the pathogenesis and therapy of psoriasis suggest the operation of a hormonal factor: (1) the frequency of onset around puberty; (2) the fact that in 50% of women patients the lesions disappear during pregnancy, although in about 15% the condition is aggravated during this period. Twelve women with generalized psoriasis of long duration, resistant to the usual treatment, were treated with progesterone given in intramuscular injections every 3 days, or in the form of subcutaneous pellets. Young patients received the drug during the 2nd phase of the menstrual cycle (200 to 300 mg. for each cycle). Postmenopausal patients were treated continuously. The only other treatment given during this study was vaseline to alleviate excessive dryness of the skin. Four patients completed the treatment, having taken a total dose of 650 to 950 mg. of progesterone. The lesions disappeared completely in 3 of them, but remained unchanged in 1. Eight patients were still under treatment when this paper was written, gradual improvement being observed in 7. Clearing of the psoriasis lesions started within the first 7 to 10 days of treatment in some patients, although in most of them it became noticeable within 4 to 8 weeks.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.

1960 *Clinical Meeting*, Washington, D. C., Nov. 28-Dec. 1.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-30.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 26-29.
1963 Annual Meeting, Atlantic City

AMERICAN

1960

August

AMERICAN ASSOCIATION OF BLOOD BANKS, Jack Tar Hotel, San Francisco, Aug. 21-26. For information write: AABB Central Office, Suite 1619, 30 N. Michigan, Chicago 2.

AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION, Mayflower Hotel, Washington, D. C., Aug. 21-26. Mrs. Dorothea C. Augustin, 30 N. Michigan Ave, Chicago 2, Executive Secretary.

AMERICAN HOSPITAL ASSOCIATION, Civic Auditorium, San Francisco, Aug. 27-Sept. 1. Mr. Maurice J. Norby, 840 N. Lake Shore Dr., Chicago 11, Secretary.

AMERICAN INSTITUTE OF ULTRASONICS IN MEDICINE, Statler-Hilton Hotel, Washington, D. C., Aug. 20. Dr. Dorothy M. Stillwell, Dept. of Phys. Med. and Rehab., Univ. of Colorado Med. Center, Denver 20, Chairman.

AMERICAN PHYSIOLOGICAL SOCIETY, Stanford University, Calif., Aug. 22-26. Mr. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

AMERICAN SOCIETY OF CLINICAL HYPNOSIS, Miami, Fla., Aug. 7-10. Dr. Seymour Hershman, 6770 N. Lincoln Ave., Chicago 46, Secretary.

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, University of Washington, Seattle, Aug. 21-25. Dr. Karl H. Beyer, Merck Sharp & Dohme Research Laboratories, West Point, Pa., Secretary.

AMERICAN VETERINARY MEDICAL ASSOCIATION, *Denver-Hilton Hotel*, Denver, Aug. 15-18. H. E. Kingman Jr., 600 S. Michigan Avenue, Chicago 5, Executive Secretary.

BIOLOGICAL PHOTOGRAPHIC ASSOCIATION, INC., Utah Motor Lodge, Salt Lake City, *Utah*, Aug. 23-26. Miss Jane H. Waters, Box 1668, Grand Central P. O., New York 17, Executive Secretary.

CONFERENCE ON THE CHEMICAL ORGANIZATION OF CELLS: NORMAL AND ABNORMAL, University of Wisconsin, Madison, Aug. 25-27. Dr. J. F. A. McManus, Dept. of Pathology, University of Alabama Medical Center, Birmingham, Chairman.

GERONTOLOGICAL SOCIETY, INC., Mark Hopkins Hotel, San Francisco, Aug. 7-12. Mrs. Marjorie Adler, 660 S. Kingshighway Blvd., St. Louis 10, Administrative Secretary.

NATIONAL MEDICAL ASSOCIATION, INC., Penn-Sheraton Hotel, Pittsburgh, Aug. 8-11. Dr. John T. Givens, 1108 Church St., Norfolk, Va., Executive Secretary.

RENO SURGICAL SOCIETY, Mapes Hotel, Reno, *Nev*, Aug. 18-20. Dr. Gilbert G. Lenz, 505 S. Arlington Ave., Reno, *Nevada*.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY, Denver-Hilton Hotel, Denver, Aug. 11-13. Dr. John H. Freed, 4200 E. 9th Ave., Denver 20, Secretary-Treasurer.

ST. JOSEPH'S HOSPITAL ANNUAL CLINICS, St. Joseph's Hospital, Denver, Aug. 3-5. Dr. W. H. Leitch, St. Joseph's Hospital, 1818 Humboldt St., Denver 18, Chairman.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, *The Greenbrier*, White Sulphur Springs, Aug. 25-27. Mr. Charles Lively, Box 1031, Charleston 24, W. Va., Executive Secretary.

September

AMERICAN ACADEMY OF PEDIATRICS, AND AMERICAN ACADEMY OF GENERAL PRACTICE, LOUISIANA CHAPTER, Roosevelt Hotel, New Orleans, Sept. 23. Dr. Herbert B. Rothschild, 1520 Louisiana Ave., New Orleans 15, Chairman of Publicity Committee.

AMERICAN MEDICAL WRITERS' ASSOCIATION, Hotel Morrison, Chicago, Sept. 30-Oct. 1. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

AMERICAN ROENTGEN RAY SOCIETY, Ambassador Hotel, Atlantic City, Sept. 27-30. Mr. Hugh Jones, 20 N. Wacker Dr., Chicago 6, Director, Public Relations.

AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS, *Palmer House*, Chicago, Sept. 24-Oct. 2. Mr. Claude E. Wells, 445 Lake Shore Drive, Chicago 11, Executive Secretary.

COLLEGE OF AMERICAN PATHOLOGISTS, Palmer House, Chicago, Sept. 24-27. Dr. Arthur H. Dearing, 2115 Prudential Plaza, *Chicago*, Executive Director.

COLORADO STATE MEDICAL SOCIETY, Stanley Hotel, Estes Park, Sept. 14-17. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary.

DELAWARE, MEDICAL SOCIETY OF, Rehoboth, Del., Sept. Mr. Lawrence C. Morris Jr., 1925 Lovering Ave., Wilmington 6, Del., Executive Secretary.

FLYING PHYSICIANS ASSOCIATION, third clinical meeting, Western Hills Lodge, Wagoner, Okla., Sept. 6-9. For information write: Flying Physicians Association National Headquarters, P. O. Box 3275, Tulsa, Okla.

INTER-SOCIETY CYTOLOGY COUNCIL, Palmer House, Chicago, Sept. 23-25. Dr. Paul A. Younge, 1101 Beacon St., Brookline 46, Mass., Secretary.

KENTUCKY STATE MEDICAL ASSOCIATION, Louisville, Sept. 20-22. Mr. J. P. Sanford, 1169 Eastern Parkway, Louisville 17, Ky., Executive Secretary.

MARYLAND, MEDICAL AND CHIRURGICAL FACULTY OF THE STATE OF, Semiannual Meeting, Ocean City, Sept. 16. Mr. John Sargeant, 1211 Cathedral St., Baltimore 1, Executive Secretary.

MICHIGAN STATE MEDICAL SOCIETY, Detroit, week of Sept. 25. Dr. D. Bruce Wiley, 606 *Townsend* St., Lansing 15, Mich., Secretary.

MONTANA MEDICAL ASSOCIATION, Baxter Hotel, Bozeman, Sept. 15-17. Dr. William E. Harris, 114 N. Second, Livingston, Montana, Secretary.

NATIONAL CANCER CONFERENCE, AMERICAN CANCER SOCIETY, INC., AND THE NATIONAL CANCER INSTITUTE, Minneapolis, Minnesota, Sept. 13-15. Dr. Roald M. Grant, 521 W. 57th St., New York 19, Coordinator.

NATIONAL RECREATION CONGRESS, Shoreham Hotel, Washington, D. C., Sept. 25-29. Willard B. Stone, 8 W. Eighth St., New York 11, Secretary.

NEVADA STATE MEDICAL ASSOCIATION, Stardust Hotel, Las Vegas, Sept. 7-10. Mr. Nelson B. Neff, P. O. Box 2790, Reno, Nev., Executive Secretary.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS, Bretton Woods, N. H., Sept. 18-19. Dr. Thomas K. Burnap, P. O. Box 81, Kenmore Station P. O., Boston 15.

OREGON STATE MEDICAL SOCIETY, Portland, Sept. 7-9. Mr. Roscoe K. Miller, 2164 S. W. Park Place, Portland 5, Ore., Executive Secretary.

PACIFIC DERMATOLOGIC ASSOCIATION, Empress Hotel, Victoria, British Columbia, Canada, Sept. 1-4. Dr. Edward J. Ringrose, 2636 Telegraph Ave., Berkeley 4, *Calif.*, Secretary-Treasurer.

SOCIETY FOR PEDIATRIC RADIOLOGY, Ambassador Hotel, Atlantic City, N. J., Sept. 26. Dr. Richard G. Lester, 412 Union St., S. E., Minneapolis 14, Minn,, Secretary-Treasurer.

SOUTHERN TRUDEAU SOCIETY (AND SOUTHERN TUBERCULOSIS CONFERENCE), Hotel Francis Marion, Charleston, S. C., Sept. 14-16. Mr. Judson M. Allred Jr., P. O. Box 9865, Northside Station, Jackson, Miss., Secretary-Treasurer.

TENNESSEE VALLEY MEDICAL ASSEMBLY, Read House, Chattanooga, Tenn., Sept. 26-27. Dr. Robert A. Waters, 109 Medical Arts Bldg., Chattanooga, Chairman.

TRI-STATE MEDICAL ASSEMBLY, Captain Shreve Hotel, Shreveport, La., Sept. 14-15. Dr. J. W. Wilson Jr., 940 Margaret Place, Shreveport, La., Secretary-Treasurer.

UTAH STATE MEDICAL ASSOCIATION, Hotel Utah Motor Lodge, Salt Lake City, Sept. 20-23. Mr. Harold Bowman, 42 S. 5th East, Salt Lake City 2, Executive Secretary.

WASHINGTON STATE MEDICAL ASSOCIATION, Seattle, Sept. 25-28. Mr. Ralph W. Neill, 1309 Seventh Ave., Seattle 1, Executive Secretary.

WYOMING STATE MEDICAL SOCIETY, Jackson Lake Lodge, Moran, Sept. 7-10. Mr. Arthur R. Abbey, P. O. Box 2036, Cheyenne, Wyo., Executive Secretary.

October

ACADEMY OF PSYCHOSOMATIC MEDICINE, Benjamin Franklin Hotel, Philadelphia, Oct. 13-15. For information write Dr. Bertram B. Moss, 55 E. Washington, Chicago 2.

AMERICAN ACADEMY FOR CEREBRAL PALSY, Penn-Sheraton Hotel, Pittsburgh, Oct. 5-8. Dr. Joseph D. Russ, 1520 Louisiana Ave., New Orleans 15, Executive Secretary.

AMERICAN ACADEMY OF OPHTHALMOLOGY & OTOLARYNGOLOGY, Palmer House, Chicago, Oct. 9-14. Dr. William L. Benedict, 15 Second St., S. W., Rochester, Minn., Executive Secretary.

AMERICAN ACADEMY OF PEDIATRICS, Palmer House, Chicago, Oct. 17-20. Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.

AMERICAN ASSOCIATION OF MEDICAL CLINICS, New Orleans, Oct. 6-8. Dr. Joseph B. Davis, 134 N. Washington St., Marion, Ind., Secretary.

AMERICAN ASSOCIATION OF MEDICAL RECORD LIBRARIANS, Olympia Hotel, Seattle, Oct. 10-13. Miss Doris Gleason, 840 N. Lake Shore Dr., Chicago 11, Executive Director.

AMERICAN ASSOCIATION OF POISON CONTROL CENTERS, Palmer House, Chicago, Oct. 18. Dr. Harry C. Shirkey, 712 S. 30th St., Birmingham, Ala., Chairman, Program Committee.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA, Coronado Hotel, Coronado, Calif., Oct. 5-7. Dr. William T. Fitts Jr., 3400 Spruce St., Philadelphia 4, Secretary.

AMERICAN COLLEGE OF GASTROENTEROLOGY, Bellevue-Stratford Hotel, Philadelphia, Oct. 23-26. Mr. Daniel Weiss, 33 W. 60th St., New York 23, Executive Director.

AMERICAN COLLEGE OF SURGEONS, Clinical Congress, San Francisco, Oct. 10-14. For information write: Dr. William E. Adams, 40 E. Erie St., Chicago 11.

AMERICAN FRACTURE ASSOCIATION, El Presidentia Hotel, Mexico, *D. F.*, Mexico, Oct. 30-Nov. 4. Dr. H. W. Wellmerling, 610 Griesheim Bldg., Bloomington, Ill., Executive Secretary.

AMERICAN HEART ASSOCIATION, INC., Jefferson Hotel, St. Louis, Oct. 21-25. Mr. Rome A. Betts, 44 E. 23rd St., New York 10, Executive *Director*.

AMERICAN OTORHINOLOGIC SOCIETY FOR PLASTIC SURGERY, INC., *Conra* Hilton, Chicago, Oct. 9. Dr. Joseph G. Gilbert, 75 Barberry Lane, Rosly Heights, L. I., New York, Secretary.

AMERICAN PUBLIC HEALTH ASSOCIATION, *San Francisco, Oct. 30-Nov. 4*. Dr. Berwyn F. Mattison, 1790 Broadway, New York 19, Executiv Director.

AMERICAN RHINOLOGIC SOCIETY, Belmont Hotel, Chicago, Oct. 8. Dr Robert M. Hansen, 1735 N. Wheeler Ave., *Portland* 17, Ore., Secretary.

AMERICAN SCHOOL HEALTH ASSOCIATION, San Francisco, Oct. 30-Nov. 4. Dr. A. O. DeWeese, 515 E. Main St., Kent, Ohio, Executive Secretary.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., *Statler-Hilton*, New York City, Oct. 2-7. Mr. John W. Andes, *515 Busse Hwy.*, Park Ridge, Ill., Executive Secretary.